Studies on Transition-Metal Complex-Catalyzed Novel Transformation of Nitroarenes and Oximes by Deoxygenation Using Carbon Monoxide

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Acknowledgements

The studies presented in this thesis are the summaries of the author's work carried out during 1987-1992 at the Department of Hydrocarbon Chemistry, Faculty of Engineering, Kyoto University.

The author would like to express his sincerest gratitude to Professor Yoshihisa Watanabe for his invaluable guidance, suggestions, innumerous instructions and encouragement throughout the course of this study.

Heartfelt thanks go to Dr. Teruyuki Kondo for giving the author so much instructions, suggestions and encouragement which are beyond words during this study. Thanks are also due to Associate Professor Take-aki Mitsudo, and Associate Professor Yasushi Tsuji of Gifu University for their stimulative discussions. The author also wishes to express his gratitude to Dr. Kenji Wada and Mr. Shinji Kotachi for their lively discussions and encouragement. It is his great pleasure to thank Mr. Jun Yamamoto for his collaboration and all members of the research group of Professor Yoshihisa Watanabe.

Finally, the author would like to give his greatest thanks to his parents, sisters, and fiancée, Miss Yoko Nagasako, for their continuous encouragement and support throughout the present study.

December 1992

Motohiro Akazome

Contents

General Introduction

Today, chemical industry is greatly depending on petroleum as chemical and energy source, and almost all of chemical manufactures are derived from lower olefins such as ethylene, which are mainly obtained from the thermal cracking of naphtha. However, since "oil crisis" in 1973, Gulf War in 1991 and the ever-present awareness of the constant depletion of the oil reserves, it becomes an urgent problem to secure an alternative chemical and energy resource. The situation that the next few years will undoubtedly bring an increase in oil price, coupled with the uncertain political situation in several of the main oil producing countries, also gives an even greater boost to research in this field. Accordingly, the significance of C_1 chemistry represented by (coal-based) carbon monoxide has recently become even more evident.[1]

Carbon monoxide first discovered by Lassonne in heating charcoal with zinc oxide in 1776 is a colorless, odorless, highly toxic, and flammable gas, liquefying at -191.5 °C.[2] Carbon monoxide has the highest carbon-oxygen bond energy (1070 $kJmol^{-1}$ (255.7 $kcalmol^{-1}$)) among the diatomic molecules, and the bond length is 1.128 Å, which corresponds to the value of carbon-oxygen triple bond. Nowadays, a manufacturing method of carbon monoxide has been established, and carbon monoxide is made easily and inexpensively from all available carbon resources such as coal, methane, higher boiling paraffins, and discharged gas from iron foundries.[3]

It may fairly be said that the chemistry of carbon monoxide is the chemistry of organotransition metal complexes, and in particular of metal carbonyls and related complexes.[4] The major area of transition-metal complexes bearing carbon monoxide ligand originated in the work starting in 1868 by Schützenberger and later by Mond, and was subsequently developed

especially by Hieber and co-workers. Carbon monoxide is an extremely weak sigma donor ligand ("hard base"). It is, however, a good "soft" ligand and bonds quite tenaciously to transition metals. A characteristic feature of "soft", polarizable ligands such as carbon monoxide is their ability to stabilize metals in low oxidation states.[5] This property is associated with the fact that the donor atoms of these ligands possess vacant, low-lying orbitals in addition to lone pairs of electrons. Back donation of electrons from filled metal *d* orbitals to vacant, antibonding π^* orbitals on the ligand supplements the bonding arising from lone pair donation. The interaction of transition metal and carbon monoxide orbitals is illustrated in Fig. 1.

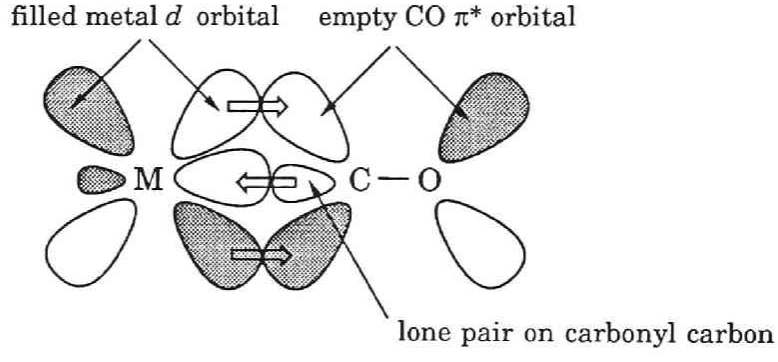


Figure 1. Interaction of transition metal and carbon monoxide orbitals

High electron density on the low-valent metal can thus be delocalized onto carbon monoxide ligand. So, coordination of carbon monoxide to transition metals produces an electronic perturbation in the carbon-oxygen bond, although the extent is dependent on many factors such as the nature of metal, its charge, oxidation state and the nature of other coordinated ligands. This perturbation generally leads to an increased reactivity of carbon monoxide towards attack by nucleophiles such as hydroxide, alkoxide and amines.

Thus, the success of the effective utilization of carbon monoxide will depend entirely upon the development of the organotransition metal chemistry, and transition-metal carbonyl species can often work as a key intermediate in the various transformations of carbon monoxide. Today, several projects using carbon monoxide as a C_1 source have been industrialized. For example, 1) hydroformylation (Oxo process, Roelen reaction)[2b,6] and hydrocarboxylation (Reppe reaction),[7] 2) carbonylation of methanol to acetic acid (Monsanto's process),[8] 3) ethylene glycol synthesis,[9] and 4) hydrogenation of carbon monoxide including Fischer-Tropsch (F-T) synthesis.[10]

On the other hand, an alternative reactivity of carbon monoxide is its high reducing, *i.e.*, deoxygenative, ability. For example, water gas shift (WGS) reaction catalyzed by transition-metal complexes can be regarded as the deoxygenation of water to hydrogen by carbon monoxide (eq 1).[11] Now, WGS reaction was used industrially to prepare various molar ratios of CO/H_2 gas (syn gas), since the ratios of CO/H_2 in syn gas are important when considering further conversion processes of syn gas. For instance, syn gas for methanol manufacture requires a CO/H_2 molar ratio of 1:2, and syn gas for hydroformylation requires a CO/H_2 molar ratio of 1:1. The CO/H_2 molar ratio can be adjusted to that required by use of WGS reaction, which is carried out commercially over supported metal oxide catalysts at elevated temperatures.[11]

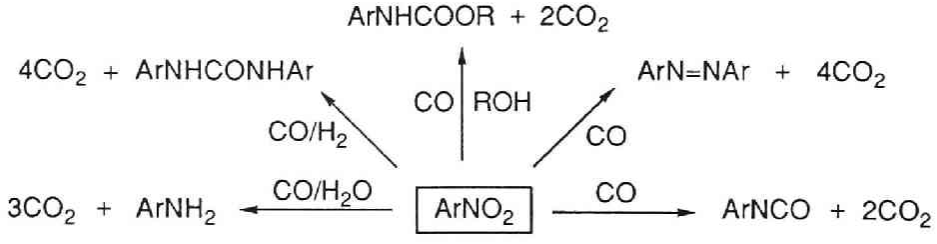
$$CO + H_2O \xrightarrow{\text{Cat.}} CO_2 + H_2 \qquad (1)$$

The other reaction using deoxygenating ability of carbon monoxide is the reductive *N*-carbonylation of nitroarenes to isocyanates or carbamates.[12] The conversion of nitroarenes to the corresponding isocyanates is of considerable interest, since the latter are the raw materials for polyurethane manufacture. The classical method of this conversion is via catalytic hydrogenation of

nitroarenes to aminoarenes and subsequent reaction of aminoarenes with phosgene (eq 2).

$$ArNO_2 + 3H_2 \longrightarrow ArNH_2 + 2H_2O$$
$$ArNH_2 + COCl_2 \longrightarrow ArNCO + 2HCl \qquad (2)$$

During the last decade, considerable research work has been expended on finding new, phosgene-free routes to aromatic isocyanates, *i.e.*, reductive *N*-carbonylation of nitroarenes to isocyanates. As can be readily seen from Scheme 1, various nitrogen containing compounds such as isocyanates, azo compounds, carbamates, ureas and aminoarenes can be now successfully synthesized in good yields and selectivities by transition-metal complex-catalyzed reduction and/or reductive transformations of nitroarenes including reductive *N*-carbonylation reaction.



Scheme 1. Reductive transformations of nitrobenzene using carbon monoxide

These reactions can be rationalized by assuming a nitrene intermediate[13] generated from the deoxygenative reduction of nitroarenes. If this reactive nitrene intermediate is efficiently trapped by unsaturated functional groups such as C=N, C=C and C=O groups at the *ortho*-position from the nitro substituent on an aromatic ring, novel catalytic syntheses of various *N*-heterocyclic compounds can be constructed.

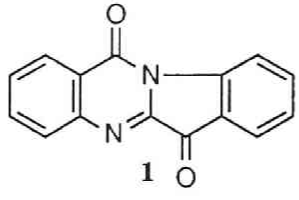
Heterocyclic compounds, especially *N*-heterocyclic compounds, are very widely distributed in Nature and a large number of these compounds are essential to life, since they play a vital role in the metabolism of all living cells.[14] For example, tryptophan, which has an indole nucleus, is one of the essential amino acids for human being and domestic animals.[15] Indole-3-acetic acid, a kind of auxin, is used as a growth hormone of plant in an agricultural field. Indomethacine has been used as a new class of anti-inflammatory and antipyretic agent since 1960's.[15,16] Quinazolinones and quinazolines are important as quinazolinone alkaloids. Pyrimidines are extremely important building block of purine bases[17] as well as agricultural chemicals. Thus, heterocyclic compounds are indispensable for the various fields of pharmacology, agriculture and chemical industry, and transition-metal complexes have recently been used to prepare a great variety of heterocyclic ring systems.[18] Although the effective use of carbon monoxide as a C_1 source in various carbonylation reactions has been fully studied and established as mentioned above, the study on utilization of carbon monoxide as a reducing agent in the synthesis of *N*-heterocyclic compounds or other nitrogen containing compounds has been strictly limited. So the author directed his attention to developing transition-metal complex-catalyzed novel syntheses of various *N*-heterocyclic compounds from *ortho*-substituted nitroarenes via reductive *N*-heterocyclization reaction, and novel transformations of oximes via deoxygenative reduction using carbon monoxide, with a final object to developing a new field of the chemistry of carbon monoxide, *viz.*, C_1 chemistry, and to exploring these reactions to the point where they can be regarded as routine, general synthetic methods.

This thesis is divided into two parts. Part I, which comprises chapters 1 to 4, deals with palladium and ruthenium complex-catalyzed novel reductive *N*-heterocyclization of nitroarenes bearing C=N, C=C, and C=O groups at *ortho*-position from the nitro substituent on an aromatic ring using carbon monoxide as a deoxygenating agent. In this part, we developed novel catalytic syntheses of 2*H*-indazole, indole, 4(3*H*)-quinazolinone and quinazoline derivatives from *N*-(2-nitrobenzylidene)amines, *o*-nitrostyrenes, *N*-(2-nitrobenzoyl)amides, and 2-nitrobenzaldehydes or 2-nitrophenyl ketones, which are easily available raw materials. In a series of these palladium and ruthenium-catalyzed reductive *N*-heterocyclization reactions, a common key intermediate would be a transition-metal nitrene complex,[13] which seems to be generated from the deoxygenative reduction of *ortho*-substituted nitroarenes by carbon monoxide.

Chapter 1 deals with palladium complex-catalyzed reductive *N*-heterocyclization of *N*-(2-nitrobenzylidene)amines into 2*H*-indazole derivatives.[19] The combination of palladium complex with tin (II) chloride was essential for the catalytic activity. This reaction is quite attractive as a transition-metal complex-catalyzed selective nitrogen-nitrogen bond forming reaction.

In chapter 2, novel synthesis of indoles via palladium-catalyzed reductive *N*-heterocyclization of *o*-nitrostyrene derivatives is described.[20] As mentioned above, much attention has been paid to the selective synthesis of various indole derivatives because of their biological importance. Here, we have found that the palladium complex-tin (II) chloride catalyst system also promoted the reductive *N*-heterocyclization of *o*-nitrostyrene derivatives into indole derivatives effectively. This reaction offers a novel synthetic method of indoles under *neutral* reaction conditions.

In chapter 3, synthesis of 4(3*H*)-quinazolinone derivatives from *N*-(2-nitrobenzoyl)amides via transition-metal complex-catalyzed reductive *N*-heterocyclization is developed.[21] Recently, interest in many of quinazolinone alkaloids such as tryptanthrine (**1**),[22] vasicinone,[23] and rutaecarpine[24] has also been stimulated because of their biological activities. However, the catalytic synthesis of these quinazolinones was little known. In this chapter, we disclose a first example of ruthenium-catalyzed direct synthesis of 4(3*H*)-quinazolinone derivatives from *N*-(2-nitrobenzoyl)amines under carbon monoxide pressure. The present method can be applied to one-pot synthesis of indolo[2,1-*b*]-quinazoline-6,12-dione (**1**), which is well-known as antibiotic tryptanthrine.



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Chapter 4 deals with palladium complex-catalyzed intermolecular reductive *N*-heterocyclization of 2-nitrobenzaldehydes or 2-nitrophenyl ketones with formamide into quinazoline derivatives. Since Griess reported the first synthesis of 2-cyano-3,4-dihydro-4-oxoquinazoline by the reaction of cyanogen with anthranilic acid in 1869,[25] a large number of quinazoline derivatives have been synthesized. Now, we successfully developed a novel synthesis of quinazolines via palladium-catalyzed reductive *N*-heterocyclization of 2-nitrobenzaldehydes or 2-nitrophenyl ketones using formamide as a C-N unit of quinazoline ring. In the present reaction, palladium complex combined with molybdenum (V) chloride showed the highest catalytic activity.

Part II, which is composed of chapters 5 to 7, deals with ruthenium complex-catalyzed novel transformation of oximes by deoxygenative reduction using carbon monoxide. Since oximes are easily prepared from various

carbonyl compounds and hydroxylamine, but its utilization is limited to the synthesis of lactams via Beckmann rearrangement,[26] we also made an effort to develop novel deoxygenative transformations of oximes.

Chapter 5 deals with ruthenium complex-catalyzed selective deoxygenation of ketoximes to ketimines.[27] The present reaction provides *N*-nonsubstituted ketimines and successfully leaves a C=N bond. This type of reduction can be accomplished by only use of carbon monoxide, and the reduction of ketoximes using hydrogen leads to the complete reduction to give the corresponding amines. After the reaction, a stoichiometric amount of carbon dioxide was detected in a gas phase. In contrast to ketoximes, however, aldoximes were only dehydrated to the corresponding nitriles under the same reaction conditions.

Chapter 6 describes that $Ru_3(CO)_{12}$ catalyst-carbon monoxide system can be applied to the selective deoxygenation of amidoximes to amidines.[28] In the field of antibiotics, the amidine is one of the most important functional compounds, which is contained in the structures of amidinomycin, noformycin, and netropsin. The starting amidoximes are easily derived from the corresponding nitriles and hydroxylamine. With controlling the reaction conditions (reaction temperature and carbon monoxide pressure), various amidines can be synthesized selectively in good yields. Furthermore, in the presence of 1,3-dicarbonyl compounds, deoxygenation of amidoximes and subsequent condensation of the generated amidines with 1,3-dicarbonyl compounds afforded the corresponding pyrimidine derivatives in high yields.[28]

Chapter 7 deals with ruthenium complex-catalyzed allylation of a C=N bond in amidoximes with allylic carbonates via deoxygenation of aldoximes. This reaction is the first example of *catalytic* allylation of the C=N bond and afforded the corresponding homoallylic amines in moderate to good yields. In

contrast to electrophilic π-allylpalladium and platinum complexes,[29] a π-allylruthenium intermediate, which seems to be the most plausible key intermediate in the present reaction, acts as a nucleophile rather than as an electrophile as in our previously reported ruthenium-catalyzed allylation of aldehydes[30] and alcohols.[31] Indeed, when palladium or platinum catalyst instead of ruthenium catalyst was employed in the reaction of benzaldoxime with allyl methyl carbonate, only selective *O*-allylation of benzaldoximes smoothly proceeded and the corresponding *O*-allylated benzaldoxime was obtained in good yield. However, in the reaction with ketoximes, only deoxygenation of ketoximes to ketimines proceeded as in chapter 5.

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Part I Transition-Metal Complex-Catalyzed Reductive *N*-Heterocyclization of *o*-Substituted Nitroarenes Using Carbon Monoxide

Chapter 1

Palladium Complex-Catalyzed Reductive *N*-Heterocyclization of *N*-(2-Nitrobenzylidene)amines into 2*H*-Indazole Derivatives[1]

[Summary]

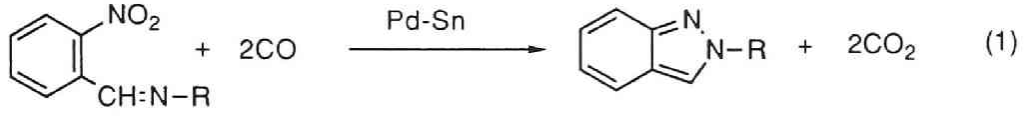
Dichlorobis(triphenylphosphine)palladium ($PdCl_2(PPh_3)_2$) tin(II) chloride ($SnCl_2$) system shows a high catalytic activity for the reductive *N*-heterocyclization reaction of various *N*-(2-nitrobenzylidene)amines at 100 °C for 16 h under an initial carbon monoxide pressure of 20 $kgcm^{-2}$ to give the corresponding 2*H*-indazole derivatives in moderate to good yields. In the reaction of *N*-(2-nitrobenzylidene)propylamine, 2-propyl-2*H*-indazole was obtained in 83% yield. Furthermore, 2,1-benzisoxazole was obtained in 37 % yield from 2-nitrobenzaldehyde. Carbon monoxide as a reducing agent of the nitro group is essential for the present reductive *N*-heterocyclization reaction.

[Introduction]

Although many interests in chemistry of pyrazole and indazole derivatives have been stimulated because of their applications in industry and agriculture, and because of their biological and analytical importance, little is known about the catalytic synthesis of these compounds.[2] Most widely adapted synthetic methods of 2*H*-indazole derivatives are the reduction of *N*-(2-nitrobenzylidene)amines using triethylphosphite as a reducing agent[3a] and thermal decomposition of *N*-(2-azidobenzylidene)amines.[3b] Among the various possible methods for the construction of *N*-heterocyclic skeletons, we feel a great interest in transition-metal complex-catalyzed reductive *N*-heterocyclization[4] as well as reductive *N*-carbonylation[5] of nitro compounds using carbon monoxide as a reducing agent. Recently, Cenini et al. reported transition-metal carbonyl complex-catalyzed reductive *N*-heterocyclization of *o*-nitrostyrenes and 2-nitroazobenzenes into indoles[6] and benzotriazoles[7] respectively. However, the reaction conditions were very severe. In this chapter, we wish to disclose a novel palladium-catalyzed synthesis of 2*H*-indazoles from *N*-(2-nitrobenzylidene)amines via a reductive *N*-heterocyclization under relatively mild conditions, *i.e.*, under 20 $kgcm^{-2}$ of carbon monoxide pressure at 100 °C.[1] The present reaction is quite attractive since it can be regarded as a transition-metal complex-catalyzed selective nitrogen-nitrogen bond forming reaction between the nitro group and imino group. It is remarkably different from iron pentacarbonyl-catalyzed reductive homo-coupling of nitroarenes into azo- and/or azoxycompounds.[8] In the reaction of 2-nitrobenzaldehyde, a similar nitrogen-oxygen bond forming reaction proceeded to give 2,1-benzisoxazole in 37% yield.

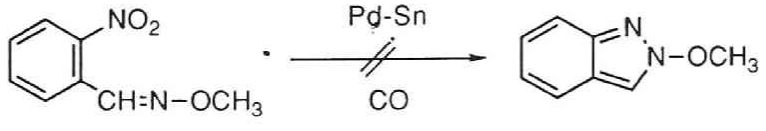
[Results and Discussion]

The reductive *N*-heterocyclization of *N*-(2-nitrobenzylidene)amines smoothly proceeded by the catalyst system of a palladium complex combined with $SnCl_2$ under carbon monoxide pressure to give the corresponding 2*H*-indazole derivatives (eq 1).



(1)

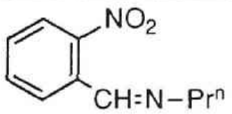
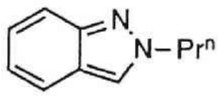
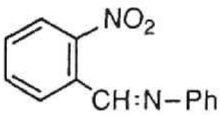
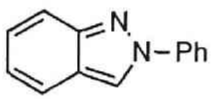
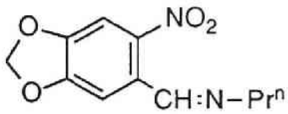
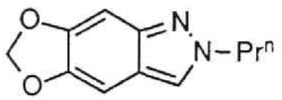
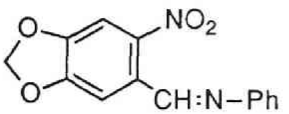
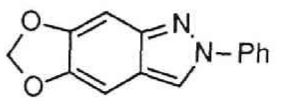
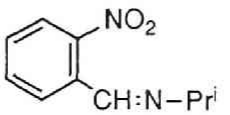
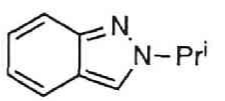
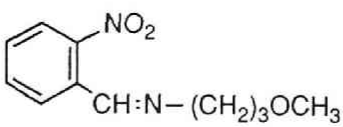
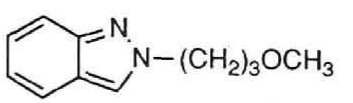
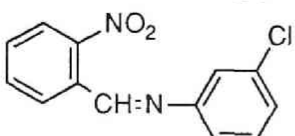
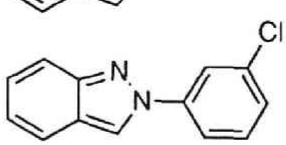
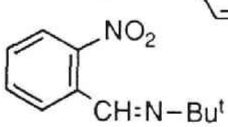
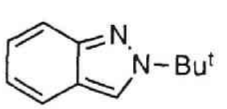
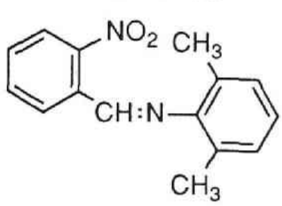
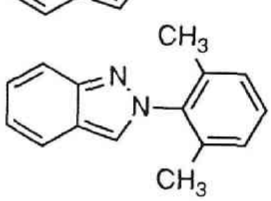
Results are listed in Table I. As for the substituents on the imino group, alkyl, phenyl, 3-chlorophenyl, and methoxyalkyl groups were acceptable and the corresponding 2*H*-indazole derivatives were obtained in 51-83 % yields (Runs 1-7). Especially, the steric hindrance of subtituents on the nitrogen atom of the imino group such as tert-butyl and 2,6-dimethylphenyl substituents did not affect the present reaction (Runs 8 and 9). Although 2*H*-indazole derivatives having a dioxymethylene substituent on the aromatic ring were obtained in good yields (Runs 3 and 4), 2-nitrobenzaldehyde oxime *O*-methyl ether did not give the corresponding 2*H*-indazole at all (eq 2). This heteroatom substituent on the imino group prevented from proceeding the present reductive *N*-heterocyclization reaction.



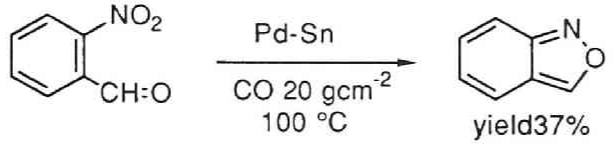
(2)

In the employment of 2-nitrobenzaldehyde instead of *N*-(2-nitrobenzylidene)amines, 2,1-benzisoxazole was obtained in 37% yield under the present reaction conditions (eq 3).

Table I. Reductive *N*-Heterocyclization of *N*-(2-Nitrobenzylidene)amines[a]

Run	Substrate	Product	Yield/%[b]
1			62 (83)
2			48 (64)
3			65
4			51
5			63
6			53
7			74
8			75
9			59

a) *N*-(2-Nitrobenzylidene)amine (2.0 mmol), $PdCl_2(PPh_3)_2$ (0.10 mmol), $SnCl_2$ (1.0 mmol), THF (10 ml) under CO (20 $kgcm^{-2}$) at 100 °C for 16 h.
b) Isolated yields (GLC yields).



(3)

The catalytic activities of several transition-metal complexes are examined in the reductive *N*-heterocyclization of *N*-(2-nitrobenzylidene)-aniline, and the results are summarized in Table II. The combination of $PdCl_2(PPh_3)_2$ with $SnCl_2$ was essential for the catalytic activity (Runs 10-14). Although the catalytic activity of zerovalent palladium complex ($Pd(PPh_3)_4$) was low, the combination of $Pd(PPh_3)_4$ with $SnCl_2$ also drastically improved the catalytic activity (Runs 14 and 15). The catalyst system of $PtCl_2(PPh_3)_2$ combined with $SnCl_2$ also showed a moderate catalytic activity (Run 16), but the catalytic activities of other group VIII metal complexes were quite low (Runs 20-22).

As for the effect of additives, especially Lewis acids, both $SnCl_2$ and $SnCl_4$ were efficient for the present reaction (Runs 10 and 23 in Table III). Although it has already been reported that Lewis acids can promote the reduction of nitro compounds in some transition-metal complex catalyzed reductive *N*-carbonylation and *N*-heterocyclization reactions, the roles of Lewis acids are not clarified.[5f-j,9] In the use of tin chloride, bromide, or iodide under the same conditions, the catalytic activities decreased in this order (Runs 10, 24, and 25). Other Lewis acids such as CuCl, $ZnCl_2$, $CuCl_2$, and $AlCl_3$ were ineffective (Runs 26-29). In runs 26-29, *N*-(2-nitrobenzylidene)aniline was consumed but the product was not detected at all by gas liquid chromatography, and a precipitate contaminated with residue of these Lewis acids and palladium complex was formed in the reaction mixture. The addition of $AgBF_4$ or $BF_3 \cdot Et_2O$, which could generate a cationic palladium intermediate, was also ineffective for the present reaction (Runs 30 and 31).[10]

Table II. Catalytic Activities of Several Transition-Metal Complexes[a]

Run	Catalyst	Additive	Conv./%[b]	Yield/%[b]
10	$PdCl_2(PPh_3)_2$	$SnCl_2$	100	64
11			2	0
12	$PdCl_2(PPh_3)_2$	-	13	5
13		$SnCl_2$	45	2
14	$Pd(PPh_3)_4$	$SnCl_2$	100	55
15	$Pd(PPh_3)_4$		31	6
16	$PtCl_2(PPh_3)_2$	$SnCl_2$	100	51
17	$PtCl_2(PPh_3)_2$	$SnCl_4$	100	32
18	$Pt(PPh_3)_4$	$SnCl_4$	100	18
19	$Pt(CO)_2(PPh_3)_2$	$SnCl_2$	77	8
20	$NiCl_2(PPh_3)_2$	$SnCl_2$	33	2
21	$RhCl(PPh_3)_3$	$SnCl_4$	51	3
22	$RuCl_2(PPh_3)_3$	$SnCl_2$	60	6

a) *N*-(2-Nitrobenzylidene)aniline (2.0 mmol), catalyst (0.10 mmol), additive (1.0 mmol), THF (10 ml) under CO (20 $kgcm^{-2}$) at 100 °C for 16 h. b) Determined by GLC.

Table III. Effect of Additives[a]

Run	Additive	Conv. /%[b]	Yield /%[b]
10	$SnCl_2$	100	64
23	$SnCl_4$	100	46
24	$SnBr_2$	100	29
25	SnI_2	39	14
26	CuCl	71	4
27	$ZnCl_2$	66	3
28	$CuCl_2$	100	1
29	$AlCl_3$	100	0
30	$BF_3{\cdot}Et_2O$	5	0
31	$AgBF_4$	100	0

a) *N*-(2-Nitrobenzylidene)aniline (2.0 mmol), $PdCl_2(PPh_3)_2$ (0.10 mmol), additive (1.0 mmol), THF (10 ml) under CO (20 $kgcm^{-2}$) at 100 °C for 16 h. b) Determined by GLC.

An effect of the molar ratio of tin(II) chloride to dichloro-bis(triphenylphosphine)palladium on the reductive *N*-heterocyclization of *N*-(2-nitrobenzylidene)aniline is shown in Figure 1. An addition of fivefold amount of tin(II) chloride (0.50 mmol) to the palladium complex (0.10 mml) gave the best result (conv. 100% and yield 63%). On employing twofold of tin(II) chloride, conversion and yield were 63% and 26% respectively. However, when reaction time was prolonged to 48 h on employing same twofold of tin(II) chloride, the conversion of *N*-(2-nitrobenzylidene)aniline increased to 100% and the yield of 2-phenyl-2*H*-indazole reached 43%. This result obviously means that an addition of a catalytic amount of $SnCl_2$ was sufficient for the present reaction.

After the reaction, carbon dioxide was detected in a gas phase (76 % yield), suggesting that carbon monoxide actually operates as an effective reducing agent of the nitro group. Theoretically, twofold of carbon dioxide based on *N*-(2-nitrobenzylidene)amine should be detected in a gas phase and we now speculate that $SnCl_2$ would operate not only as a Lewis acid but also as a reducing agent of the nitro group. The other reducing agents such as hydrogen (20 $kgcm^{-2}$) or water-gas shift reaction condition (water; 10 mmol, carbon monoxide pressure; 20 $kgcm^{-2}$) were totally ineffective for the present 2*H*-indazole synthesis.

The present reaction may be rationalized by assuming a nitrene intermediate (Scheme 1). Firstly, deoxygenation of the nitro group in *N*-(2-nitrobenzylidene)amine by carbon monoxide occurs to give the nitrene intermediate. This nitrene intermediate could electrophilically attack the nitrogen atom of the imino substituent to give the corresponding 2*H*-indazole derivative.[3]

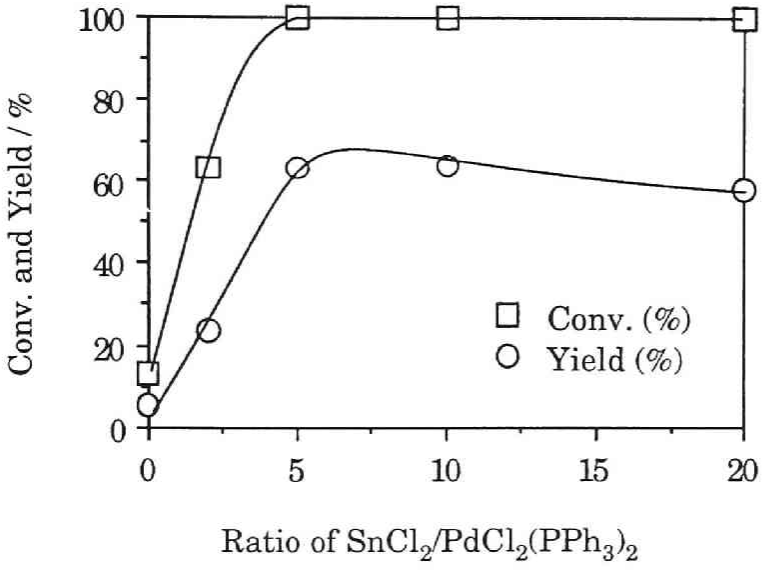
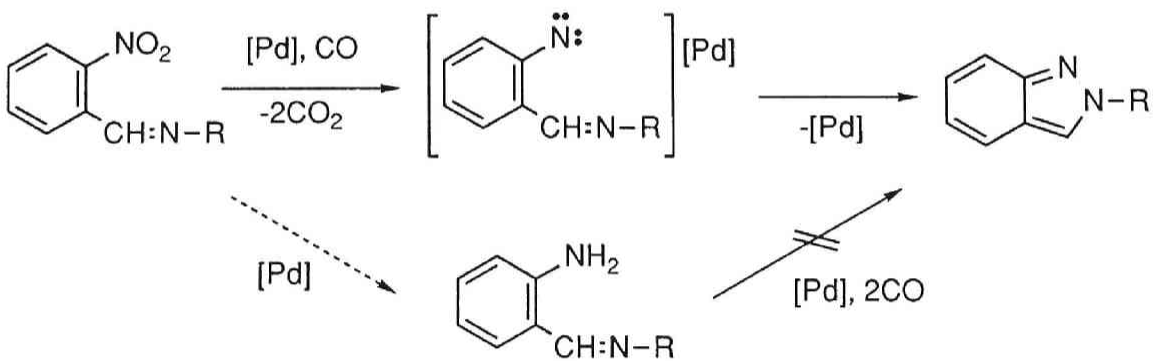


Figure 1. Effect of molar ratio of $SnCl_2/PdCl_2(PPh_3)_2$ on reductive *N*-heterocyclization of *N*-(2-nitrobenzylidene)aniline.
Reaction conditions: *N*-(2-nitrobenzylidene)aniline (2.0 mmol), $PdCl_2(PPh_3)_2$ (0.10 mmol), THF (10 ml) under CO (20 $kgcm^{-2}$) at 100 °C for 16 h.

Scheme 1



An alternative intermediate *N*-(2-aminobenzylidene)amine which would be generated by the reduction of the nitro group in *N*-(2-nitrobenzylidene)amine can be ruled out because *N*-(2-aminobenzylidene)propylamine was not transformed into 2-propyl-2*H*-indazole at all under the present reaction conditions.

Despite the current interests in the reductive *N*-carbonylaion and *N*-heterocyclization of nitroarenes, remarkably few details have been established about the mechanism of them. Recently, Metz et al. reported the generation of a metallacyclic intermediate in the reductive *N*-carbonylation of nitrobenzene.[11] In the present reaction, however, carbon monoxide operates as only a reducing agent of the nitro group and was not incorporated into the product. So, the generation of isocyanate or such metallacyclic intermediates is unlikely. Although there still remains the mechanism via nitroso intermediate,[12] we now assume a nitrene intermediate, which would strongly coordinate to the metal, in the present reaction, as postulated in many reductive *N*-carbonylation of nitroarenes[4,13] and reduction of nitroso compounds.[14]

[Experimental Section]

Materials.

The reagents employed in this study were dried and purified before use by the usual procedures. Carbon monoxide (> 99.9 %) was used without further purification. Transition-metal complexes, such as $PdCl_2(PPh_3)_2$,[15] $Pd(PPh_3)_4$,[16] $PtCl_2(PPh_3)_2$,[17] $Pt(PPh_3)_4$,[18] $Pt(CO)_2(PPh_3)_2$,[19] $NiCl_2(PPh_3)_2$,[20] $RhCl(PPh_3)_3$,[21] and $RuCl_2(PPh_3)_3$[22] were prepared by the literature's methods.

$SnCl_2$, $SnBr_2$, and $AgBF_4$ were purchased from Aldrich Chemical Company and they were used without further purification. Starting materials, *N*-(2-nitrobenzylidene)amines, were readily synthesized by a condensation of 2-nitrobenzaldehyde with the corresponding amines using $MgSO_4$ as a dehydrating reagent in ether solution.

General Procedures.

A mixture of *N*-(2-nitrobenzylidene)amine (2.0 mmol), $PdCl_2(PPh_3)_2$ (0.10 mmol), $SnCl_2$ (1.0 mmol), and dry tetrahydrofuran (THF) (10 ml) was placed in a 50 ml stainless steel autoclave (Yuasa Giken; SUS 316) equipped with a glass liner and a magnetic stirring bar. The unit was sealed and then purged three times with 10 $kgcm^{-2}$ pressurization-depressurization cycles of carbon monoxide. The reactor was then pressurized to 20 $kgcm^{-2}$ with carbon monoxide (at room temperature), and heated to 100 °C within 10 min with stirring, and held at this temperature for 16 h. The reaction was terminated by rapid cooling, and gaseous products were discharged. The resulting brown solution was analyzed by GLC and FT-IR. The products were isolated by Kugelrohr distillation and/or medium pressure column chromatography (absorbent: silica gel; eluent; a mixture of hexane and ethyl acetate). The identification of the products was confirmed by FT-IR, ^1H- and ^{13}C-NMR, elemental analyses and GC-MS. The GLC analyses were carried out on Shimadzu GC-8A chromatographs equipped with glass columns (3 mm i. d. X 3 m) packed with Silicone OV-17 (2 % on Chromosorb W(AW-DMCS), 80-100 mesh) and PEG-HT (5 % on Uniport HP, 60-80 mesh). The ^1H-NMR spectra were recorded at 90 MHz with a JEOL JNM FX-90 spectrometer and/or 270 MHz with a JEOL GSX-270 spectrometer. ^{13}C-NMR spectra were recorded at 25.05 MHz with JEOL JNM FX-100 spectrometer. Samples were dissolved in

$CDCl_3$, and the chemical shift values were expressed in relative to Me_4Si as an internal standard. Elemental analyses were performed at Microanalytical Center of Kyoto University. Mass spectra (MS) were obtained on a Shimadzu QP-2000 spectrometer. The spectral and analytical data of the products are shown below.

2-Phenyl-2*H*-indazole: white solid; mp 81.5-81.8 °C; ^{1}H NMR($CDCl_3$) δ 7.01-7.94(m, 9H, indazole, phenyl), 8.36(s, 1H, indazole, C3-H); ^{13}C NMR($CDCl_3$) δ 117.9(d, indazole, C7), 120.3(d, indazole, C4,C5), 120.9(d, phenyl, C2), 122.4(d, indazole, C6), 122.8(s, indazole, C9), 126.8(d, indazole, C3), 127.8 (d, phenyl, C4), 129.5(d, phenyl, C3), 140.5(s, phenyl, C1), 149.7(s, indazole, C8); MS, m/z (relative intensity) 194(M^+, 100), 77(Ph^+, 28.3); Anal. Calcd for $C_{13}H_{10}N_2$: C, 80.39; H, 5.19; N, 14.42. Found: C, 80.53; H, 5.30; N, 14.40.

5,6-Methylenedioxy-2-propyl-2*H*-indazole: yellow solid; mp 98.7-99.5 °C; ^{1}H NMR($CDCl_3$) δ 0.92(t, 3H, -C*H*$_3$), 1.97(sextet, 2H, -CH_2C*H*$_2$$CH_3$), 4.24(t, 2H, -C*H*$_2$$CH_2CH_3$), 5.92(s, 2H, -OC*H*$_2$O-), 6.84(s, 1H, C7-H), 6.98(s, 1H, C4-H), 7.66(s, 1H, C3-H) ; ^{13}C NMR($CDCl_3$) δ 11.1(q, CH_3), 23.8(t, -CH_2C*H*$_2$$CH_3$), 54.9(t, -*C*H$_2$$CH_2CH_3$), 93.9(d, C7), 94.7(d, C4), 116.6(s, C9), 121.8(d, C3), 144.9(s, C5), 145.6(s, C6), 148.4(s, C8); MS, m/z (relative intensity) 204(M^+, 46.6), 175(M^+-Et, 100), 162(M^+-Pr, 62.8); Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.95; N, 13.72; O, 15.67. Found: C, 64.61; H, 5.88; N, 13.67.

2-Propyl-2*H*-indazole: colorless liquid; bp 102 °C/ 1.8 mmHg(Kugelrohr distillation); ^{1}H NMR($CDCl_3$) δ 0.90(t, 3H, -C*H*$_3$), 1.99(sextet, 2H, -CH_2C*H*$_2$$CH_3$), 4.31(2H, t, -C*H*$_2$$CH_2CH_3$), 6.95-7.76(m, 4H, indazole), 7.86(s, 1H, indazoleC3-H); ^{13}C NMR($CDCl_3$) δ 11.2(q, -*C*H$_3$), 24.0(t, -CH_2*C*H$_2$$CH_3$), 55.2(t, -*C*H$_2$$CH_2CH_3$), 117.3(d, C7), 120.0(d, C5), 121.4(d, C4), 121.6(s, C3a), 122.5(d, C6), 125.6(d, C3),

148.8(s, C3a); MS, m/z (relative intensity) 160(M^+, 44.3), 131(M^+-Et, 96.1), 118(M^+-Pr, 100); Anal. Calcd for $C_{10}H_{12}N_2$: C, 74.97; H, 7.55; N, 17.48. Found: C, 74.72; H, 7.59; N, 17.36.

2-Isopropyl-2*H*-indazole: colorless liquid; bp 130 °C/ 0.4 mmHg(Kugelrohr distillation); ^{1}H NMR($CDCl_3$) δ 1.60(d, 6H, -CH_3), 4.74(septet, 1H, -CH(CH_3)$_2$), 6.95-7.79(m, 4H, indazole), 7.88(s, 1H, indazoleC3-H); ^{13}C NMR($CDCl_3$) δ 23.1(q, -CH_3), 55.1(d, -CH(CH_3)$_2$), 117.1(d, C7), 119.6(d, C5), 119.8(d, C4), 121.1(d, C6,C3a), 125.3(d, C3), 147.9(s, C7a); MS, m/z (relative intensity) 160(M^+, 31.5), 118(M^+-^{i}Pr, 100); Anal. Calcd for $C_{10}H_{12}N_2$: C, 74.97; H, 7.55; N, 17.48. Found: C, 75.22; H, 7.69; N, 17.29.

2-*tert*-Butyl-2*H*-indazole: white solid; mp 56.5-57.5 °C; ^{1}H NMR($CDCl_3$) δ 1.71(s, 9H, -CH_3), 6.95-7.80(m, 4H, indazole), 8.00(s, 1H, indazoleC3-H); ^{13}C NMR($CDCl_3$) δ 30.1(q, -CH_3), 60.1(s, -C(CH_3)$_3$), 117.0(d, C7), 119.2(d, C5), 119.9(d, C4), 120.9(s, C3a), 121.1(d, C6), 125.6(d, C3), 147.6(s, C7a); MS, m/z (relative intensity) 174(M^+, 19.2), 118(M^+-^{t}Bu, 100); Anal. Calcd for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.54; H, 8.17; N, 16.19.

5,6-Methylenedioxy-2-phenyl-2*H*-indazole: white solid; mp 173-175 °C; ^{1}H NMR($CDCl_3$) δ 5.94(s, 2H, -OCH_2O-), 6.86(s, 1H, C7-H), 7.03(s, 1H, C4-H), 7.30-7.84(m, 5H, phenyl), 8.15(s, 1H, C3-H); ^{13}C NMR($CDCl_3$) δ 93.9(d, indazole, C7), 94.6(d, indazole, C4), 110.7(t, -OCH$_2$O-) 118.3(s, indazole, C3a), 119.3(d, indazole, C3), 119.7(d, phenyl, C2), 126.7(d, phenyl, C4), 129.1(d, phenyl, C3), 140.1(s, phenyl, C1), 145.7(s, indazole, C-5), 147.0(s, indazole, C-6), 149.3(s, indazole, C-8); MS, m/z (relative intensity) 238(M^+, 100), 179(24.8), 152(20.1), 77(Ph$^+$, 60.3); Anal. Calcd for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.41; H, 4.30; N, 11.75.

2-(3-Chlorophenyl)-2*H*-indazole: white solid; mp 102.5-104.0 °C; ^{1}H NMR($CDCl_3$) δ ; ^{13}C NMR($CDCl_3$) δ 117.7(d, indazole, C7), 118.4(d, phenyl, C6), 120.1(d, indazole, C4,C5), 120.9(d, phenyl, C2), 121.1(s, indazole, C3a), 122.5(d, indazole, C6), 126.9(d, indazole, C3), 127.5(d, phenyl, C4), 130.2(d, phenyl, C5), 135.1(s, phenyl, C3), 141.0(s, phenyl, C1), 149.5(s, indazole, C7a); MS, m/z (relative intensity) 230(M[^{37}Cl]$^+$, 33.2), 228.0(M[^{35}Cl]$^+$, 100), 192(20.2); Anal. Calcd for $C_{13}H_9N_2Cl$: C, 68.28; H, 3.97; N, 12.25. Found: C, 68.44; H, 3.75; N, 12.29.

2-(2,6-Dimethylphenyl)-2*H*-indazole: white solid; mp 92.3-93.0°C; ^{1}H NMR($CDCl_3$) δ 1.97(s, 6H, CH_3), 7.10-7.35(m, 5H, phenyl and indazoleC5-H,C6-H), 7.73(d, 1H, indazoleC4-H, J=8.5Hz), 7.80(dd, 1H, indazoleC7-H, J=0.7, 8.8Hz), 7.95(s, 1H, indazoleC3-H); ^{13}C NMR($CDCl_3$) δ 17.2(q, CH_3), 118.0(d, indazole, C7), 120.3(d, indazole, C5), 121.9(d, indazole, C4), 122.7(s, indazole, C3a), 124.4(d, indazole, C6),126.1(d, phenyl, C4), 128.1(d, phenyl, C3), 129.3(d, indazole, C3), 135.4(s, phenyl, C2), 139.6(s, phenyl, C1), 149.1(s, indazole, C7a); Anal. Calcd for : C, 81.05; H, 6.35; N, 12.60. Found: C, 81.28; H, 6.47; N, 12.70.

2-(3-Methoxypropyl)-2*H*-indazole: colorless liquid; bp 190 °C / 0.2 mmHg (Kugelrohr distillation); ^{1}H NMR($CDCl_3$) δ 1.99(m, 2H, -$CH_2CH_2CH_2$-), 3.31(t, 2H, -NCH_2-, J=5.9Hz), 3.31(s, 3H, -OCH_3), 4.50(t, 2H, -OCH_2-, J=6.8Hz), 7.06(ddd, 1H, C5-H, J=0.7, 6.6, 8.3Hz), 7.26(ddd, 1H, C6-H, J=0.7, 6.6,8.8Hz), 7.63(ddd, 1H, C4-H, J=0.7, 1.0, 8.3Hz), 7.71(ddd, 1H, C7-H, J=0.7, 1.0, 8.8Hz), 7.89(s, 1H, C3-H); ^{13}C NMR($CDCl_3$) δ 30.5(t, -CH_2-), 50.4(t, -NCH_2-, 58.7(q, OCH_3), 68.8(t, -OCH_2-), 117.2(d, C7), 120.1(d, C5), 121.5(d, C4), 122.4(s, C3a), 123.2(d, C6), 125.8(d, C3), 148.8(s, C7a); MS, m/z (relative intensity) 190(M$^+$, 27.2), 175(M$^+$-Me, 26.9), 132(64.4), 131(M$^+$-$CH_2CH_2OCH_3$, 100), 119(30.0); Anal.

Calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.72. Found: C, 69.41; H, 7.53; N, 14.74.

2,1-Benzisoxazole: colorless liquid; bp 150 °C / 13 mmHg (Kugelrohr distillation); ^1H NMR($CDCl_3$) δ 6.86-7.65(m, 4H, benzisoxazole), 9.13(s, 1H, C3-H); ^{13}C NMR($CDCl_3$) δ 114.7(d, C7), 117.9(s, C3a), 119.4(d, C5), 124.1(d, C4), 130.5(d, C6), 154.0(d, C3), 155.7(s, 7a); MS, m/z (relative intensity) 119(M^+, 90.2), 92(100), 64(67.1); Anal. Calcd for C_7H_5NO: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.73; H, 4.29; N, 11.89.

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Chapter 2

Novel Synthesis of Indoles via Palladium-Catalyzed Reductive *N*-Heterocyclization of *o*-Nitrostyrene Derivatives[1]

[Summary]

Indole derivatives are readily prepared from the reductive *N*-heterocyclization of *o*-nitrostyrene derivatives in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$ - $SnCl_2$ under carbon monoxide pressure (20 $kgcm^{-2}$) at 100 °C for 16 h. For example, 2-phenylindole was obtained in 75% yield by the reductive *N*-heterocyclization of *o*-nitrostilbene. In the case of *o*-nitrochalcone, 2-benzoylindole was obtained in 52% yield, accompanied with 2-phenylquinoline in 34% yield. Reaction mechanism is also discussed on the basis of the reaction sequence using deuterium labeled substrates and β,β-disubstituted-*o*-nitrosytrene derivatives.

[Introduction]

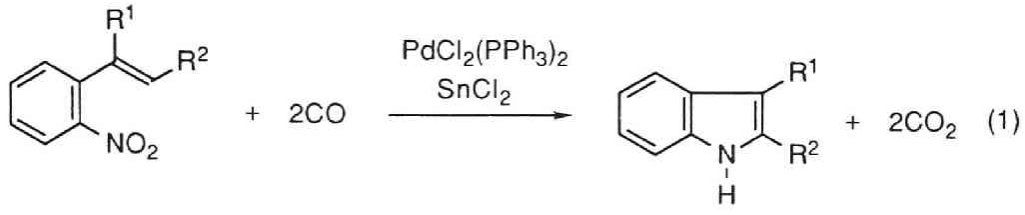
A largest number of indole derivatives are very widely distributed in the field of indole alkaloids such as strychinine, reserpine, and the ergot alkaloids.[2] These discoveries of alkaloids led the research for the significant non-steroidal anti-inflammatory agent, indomethacin,[3] and central nervous system active drug, the well-known hallucinogen lyseric acid diethylamide (LSD)[4].

As for the construction of an indole skeleton, the Fischer indole synthesis is most widely used and has been extensively reviewed.[5] Recently, numerous synthetic approaches to construction of an indole skeleton have been reported, including many employing transition-metal catalysts,[6] particularly palladium ones.[7]

Palladium complex-catalyzed indole synthesis has been reported by several research groups. Hegedus et al. have already reported the palladium (II) complex-catalyzed oxidative *N*-heterocyclization of *o*-aminostyrene or *o*-allylaniline derivatives to indole derivatives including the ergot alkaloids.[7a,b] Taniguchi et al. have reported the palladium complex-catalyzed isomerization of diphenylazirine to 3-phenylindole.[7c] Larock et al. recently reported the palladium-catalyzed heteroannulation of internal alkynes with 2-iodoanilines to indole derivatives.[7d] Although palladium complex-catalyzed reductive *N*-heterocyclization of *o*-nitrostyrene derivatives appears to be a more convenient and intriguing method, the reaction has never been reported.

Among the various synthetic methods for *N*-heterocyclic compounds, we have been interested in transition-metal complex-catalyzed reductive *N*-heterocyclization of nitroarenes.[8] In this chapter, we report a novel and facile synthesis of indoles via palladium-catalyzed reductive *N*-heterocyclization of *o*-

nitrostyrene derivatives under relatively mild reaction conditions (at 100 °C under 20 kgcm^{-2} of carbon monoxide pressure) (eq 1).



(1)

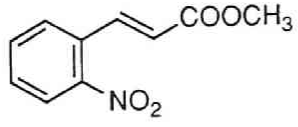
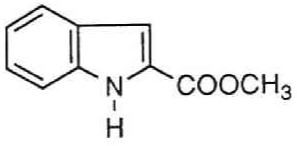
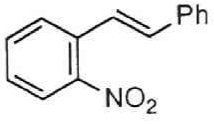
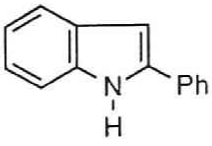
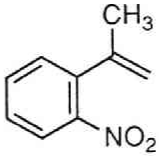
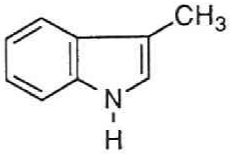
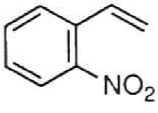
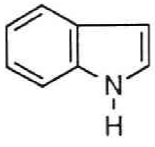
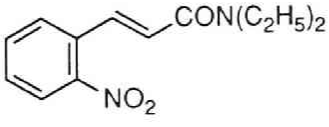
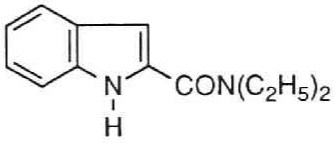
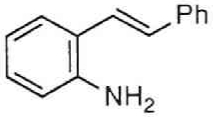
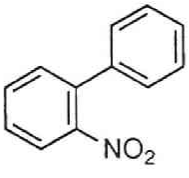
Recently, the ruthenium carbonyl complex and related complex-catalyzed reductive *N*-heterocyclization reaction, which has a similar concept but proceeded under fairly severe conditions, *i.e.*, at 220 °C under 80 kgcm^{-2} of carbon monoxide pressure, has been reported by Cenini et al.[9]

[Results and Discussion]

Reductive N-Heterocyclization of o-Nitrostyrene Derivatives

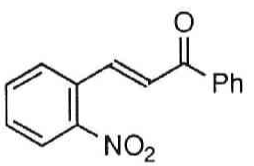
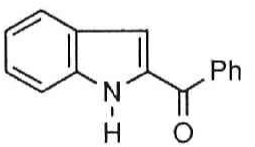
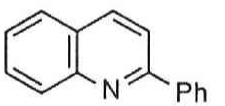
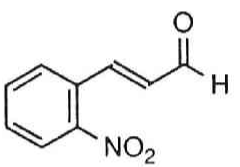
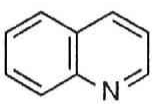
A wide variety of *o*-nitrostyrene derivatives bearing alkyl, aryl, ester, and amide groups on olefinic carbons were smoothly transformed into the corresponding indoles in 17 75% yields (Runs 1-5 in Table I). On the other hand, in the case of *o*-nitrochalcone which has an acyl group on the olefinic carbon, 2-benzoylindole was obtained in 52% yield, together with 2-phenylquinoline in 34% yield (Run 8 in Table II). In the reaction of *o*-nitrocinnamaldehyde, only quinoline was isolated in 23% yield and the corresponding indole was not obtained at all (Run 9 in Table II) (*vide infra*).

Table I. Palladium-Catalyzed Reductive *N*-Heterocyclization of *o*-Nitrostyrene Derivatives[a]

Run	Substrate	Product	Yield /%[b]
1			62 (60)
2			75 (74)
3			57 (41)
4			50
5			(17)
6		——	——
7		——	——

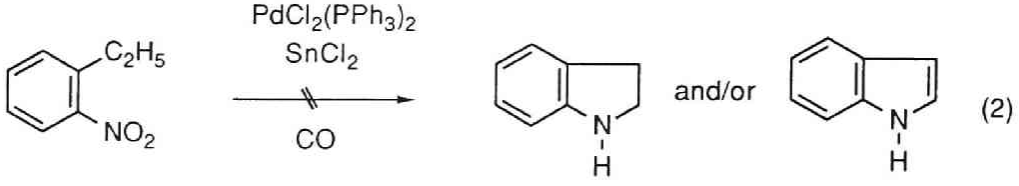
a) *o*-Nitrostyrene derivative (2.0 mmol), $PdCl_2(PPh_3)_2$ (0.10 mmol), $SnCl_2$ (1.0 mmol), 1,4-dioxane (10 ml) under CO (20kgcm^{-2}), at 100 °C for 16 h. b) GLC yields (isolated yields).

Table II. Palladium-Catalyzed Reductive *N*-Heterocyclization of *o*-Nitrochalcone and *o*-Nitrocinnamaldehyde[a]

Run	Substrate	Product and Yield/%[b]			
8			52		34
9		———			(23)

a) *o*-Nitrostyrene derivative (2.0 mmol), $PdCl_2(PPh_3)_2$ (0.10 mmol), $SnCl_2$ (1.0 mmol), 1,4-dioxane (10 ml) under CO (20 $kgcm^{-2}$) at 100 °C for 16 h. b) GLC yields (isolated yield).

Furthermore, under the present reaction conditions or even at 150 °C, *o*-nitrobiphenyl was not converted into carbazole (Run 7 in Table I). When *o*-ethylnitrobenzene was employed under the same reaction conditions at 100 °C or even at 200 °C, indole or indoline was not obtained at all, and a small amount of *o*-ethylaniline was detected at 200 °C (eq 2). As can be seen from these results, the present reductive *N*-heterocyclization reaction proceeded at only olefinic sp^2 carbons to form a C-N bond and not at sp^3 carbons directly.

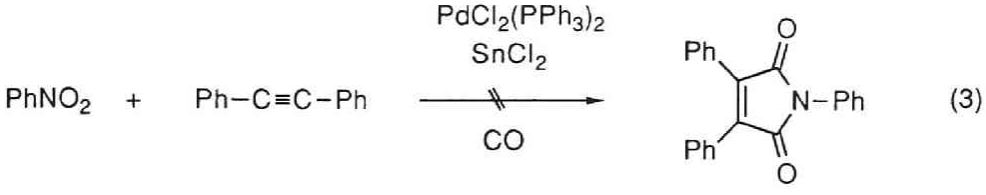


(2)

Instead of *o*-nitrostyrene, *o*-aminostyrene such as *o*-aminostilbene was employed in the present reaction, but 2-phenylindole was not obtained at all (Run 6 in Table I). This result suggests that the present reductive *N*-heterocyclization would proceed via the deoxygenation of *o*-nitrostyrenes to the corresponding nitrene intermediate and not via an *o*-aminostyrene intermediate. This consideration may also be supported by the fact that nitrobenzene did not afford aniline under the same conditions. As for *o*-aminostyrenes, Hegedus et al. have already reported the palladium(II) complex-catalyzed synthesis of indoles by intramolecular cyclization of *o*-aminostyrenes, in which *p*-benzoquinone works as a hydrogen accepter .[7b]

Recently, an intermolecular addition of a nitrene intermediate to olefins was reported and aziridines were obtained in some cases.[10] We examined a reaction of nitrobenzene with cycloheptene, but the corresponding aziridine was not obtained at all. On the other hand, Iqbal reported that the nitrene intermediate was trapped by the reaction of nitrobenzene with diphenylacetylene to give *N*-aryl diphenylmaleimide.[11] However, under the

present catalytic conditions, nitrobenzene did not react with diphenylacetylene at all (eq 3).



(3)

Gas Phase Analysis after the Reaction

After the reductive *N*-heterocyclization of methyl *o*-nitrocinnamate (Run 1), carbon dioxide evolved into a gas phase was detected in 141% yield based on methyl *o*-nitrocinnamate charged. This result suggests that carbon monoxide actually operated as an efficient reducing agent of the nitro group. Under hydrogen pressure (20 $kgcm^{-2}$) or water gas shift reaction conditions (H_2O (10 mmol) and carbon monoxide pressure (20 $kgcm^{-2}$)), the present reductive *N*-heterocyclization reaction did not proceed at all.

Comparison of Catalytic Activities of Several Transition-Metal Complexes

Catalytic activities of several transition-metal complexes were examined in the reductive *N*-heterocyclization of methyl *o*-nitrocinnamate to methyl 2-indolecarboxylate, and the results are summarized in Table III.

In the present reaction, the combination of $PdCl_2(PPh_3)_2$ with $SnCl_2$ was also essential for the catalytic activity (Runs 1, 10, and 11).[8a] Monodentate phosphorous ligands such as triphenylphosphine and tributylphosphine were also indispensable for high catalytic activity (Runs 1 and 13). However, the catalytic activity of $PdCl_2$(dppe), which bears a bidentate phosphine as a ligand, was quite low (Run 14). Other palladium complexes having 2,2'-bipyridine or benzonitrile ligands also showed low catalytic activity (Runs 15

and 16). The catalytic activity of $PdCl_2(PhCN)_2$-$SnCl_2$ system was restored to 52% yield by an addition of triphenylphosphine (Run 17). The combination of platinum complex ($PtCl_2(PPh_3)_2$) with $SnCl_2$ also showed a moderate catalytic activity (Run 19). But, the catalytic activities of other group VIII metal complexes were relatively low (Runs 20-22).

Table III. Catalytic Activities of Several Transition-Metal Complexes[a]

Run	Catalyst	Additive	Conv./%[b]	Yield/%[b]
1	$PdCl_2(PPh_3)_2$	$SnCl_2$	100	62
10	$PdCl_2(PPh_3)_2$		4	3
11		$SnCl_2$	31	7
12	$Pd(PPh_3)_4$		52	39
13	$PdCl_2(PBu_3)_2$	$SnCl_2$	81	61
14[c]	$PdCl_2$(dppe)	$SnCl_2$	31	11
15[d]	$PdCl_2$(bipy)	$SnCl_2$	16	8
16	$PdCl_2(PhCN)_2$	$SnCl_2$	14	10
17	$PdCl_2(PhCN)_2$ +$2PPh_3$	$SnCl_2$	96	52
18	$2PPh_3$	$SnCl_2$	30	10
19	$PtCl_2(PPh_3)_2$	$SnCl_2$	44	32
20	$NiCl_2(PPh_3)_2$	$SnCl_2$	31	8
21	$RuCl_2(PPh_3)_3$	$SnCl_2$	25	16
22	$RhCl(PPh_3)_3$	$SnCl_2$	24	15

a) Methyl *o*-nitrocinnamate (2.0 mmol), catalyst (0.10 mmol), additive (1.0 mmol), 1,4-dioxane (10 ml) under CO (20 $kgcm^{-2}$) at 100°C for 16 h. b) Determined by GLC. c) dppe = 1,2-bis(diphenylphosphino)ethane. d) bipy = 2,2'-bipyridine.

Effect of additives was also examined in the same reaction and summarized in Table IV.

Table IV. Effect of Additives on Reductive *N*-Heterocyclization of Methyl *o*-Nitrocinnamate[a]

Run	Catalyst	Additive	Conv./%[b]	Yield/%[b]
23	$PdCl_2(PPh_3)_2$	$SnCl_4$	23	8
24	$Pd(PPh_3)_4$	$SnCl_4$	24	8
25	$PdCl_2(PPh_3)_2$	$CuCl_2$	4	3
26	$PdCl_2(PPh_3)_2$	$FeCl_3$	4	2
27	$PdCl_2(PPh_3)_2$	$ZnCl_2$	24	2
28	$PdCl_2(PPh_3)_2$	$MoCl_5$	100	0
29	$PdCl_2(PPh_3)_2$	$AgBF_4$	11	6
30	$PdCl_2(PPh_3)_2$	$BF_3 \cdot Et_2O$	7	0
31	$PdCl_2(PPh_3)_2$	$SnBr_2$	46	23
32	$PdCl_2(PPh_3)_2$	SnI_2	35	16

a) Methyl *o*-nitrocinnamate (2.0 mmol), catalyst (0.10 mmol), additive (1.0 mmol), 1,4-dioxane (10 ml) under CO (20 $kgcm^{-2}$) at 100 °C for 16 h. b) Determined by GLC.

Although the addition of $SnCl_4$ to $PdCl_2(PPh_3)_2$ lead to moderate yield of 2*H*-indazole derivatives in our previously reported reductive *N*-heterocyclization of *N*-(2-nitrobenzylidene)amines,[8a] $SnCl_4$ was less effective in the present indole synthesis (Run 23). Similarly, the combination of $Pd(PPh_3)_4$ with $SnCl_4$ was also ineffective (Run 24). The addition of $CuCl_2$, which was used as a re-oxidizing reagent of palladium complex in the well-known Wacker process, was also ineffective (Run 25). Other Lewis acids such as $FeCl_3$, $ZnCl_2$, and $MoCl_5$ were totally ineffective (Runs 26-28). Since BF_4^- or $CF_3SO_3^-$ is a weekly or non-coordinating anion, the cationic palladium intermediate generated by an addition of these salts has more coordination sites in comparison with the same valent and neutral palladium

intermediates, and the cationic palladium complexes are often employed in organic synthesis.[12] However, an addition of $BF_3 \cdot Et_2O$ or $AgBF_4$ did not improve the catalytic activity (Runs 29 and 30). When the effect of additions of tin (II) chloride, bromide, and iodide was examined under the same reaction conditions, the catalytic activities decreased in this order (Runs 1, 31, and 32).

The effect of the molar ratio of $SnCl_2/PdCl_2(PPh_3)_2$ in the reductive *N*-heterocyclization of methyl *o*-nitrocinnamate is shown in Figure 1. When the ratio was 10, the best yield of the indole (62%) was obtained. Further addition of $SnCl_2$ did not improve the yield of the indole. In case that the ratio was 2 and reaction time was 16 hours, the conversion and yield were 90% and 36%, respectively. When the reaction time was prolonged to 48 hours under the same conditions, both the conversion and yield were improved up to 100% and 55%, respectively. This result suggests that an addition of a catalytic amount of tin (II) chloride was sufficient for the present reductive *N*-heterocyclization reaction.

Optimization of the Reaction Conditions

The present reaction was carried out in various solvents, and the results are summarized in Table V. Among the solvent employed, 1,4-dioxane was the most effective solvent, because of the high solubility of tin(II) chloride in this solvent. In 1,4-dioxane, the reaction solution was completely homogeneous after the termination of the reaction.

The optimization of reaction conditions was performed using methyl *o*-nitrocinnamate as a substrate and the effects of carbon monoxide pressure (initial pressure) and reaction temperature are illustrated in Figures 2 and 3, respectively.

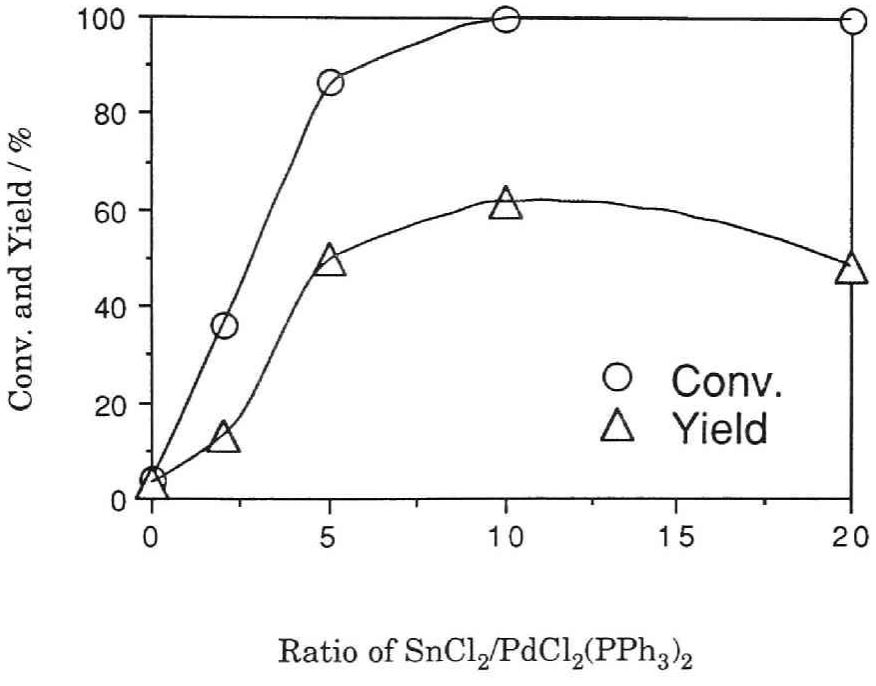


Figure 1. Effect of molar ratio of $SnCl_2/PdCl_2(PPh_3)_2$ on reductive *N*-heterocyclization of methyl *o*-nitrocinnamate. Reaction coditions: methyl *o*-nitrocinnamate (2.0 mmol), $PdCl_2(PPh_3)_2$ (0.10 mmol), 1,4-dioxane (10 ml) under CO 20 $kgcm^{-2}$ at 100 °C for 16 h.

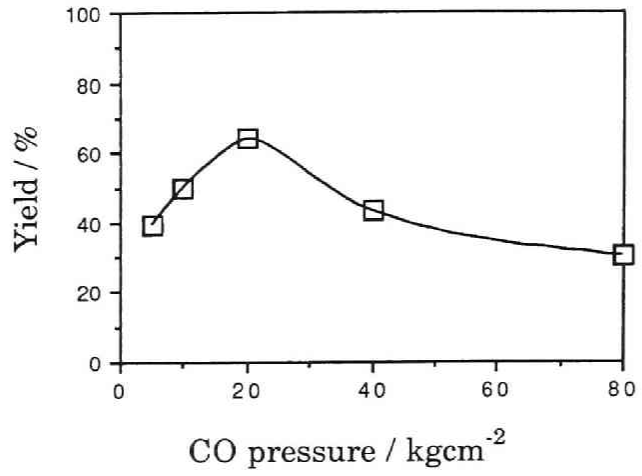


Figure 2. Effect of initial CO pressure on palladium-catalyzed reductive *N*-heterocyclization of methyl *o*-nitrocinnamate.
Reaction conditions: methyl *o*-nitrocinnamate (2.0 mmol), $PdCl_2(PPh_3)_2$ (0.10 mmol), $SnCl_2$ (1,0 mmol), and 1,4-dioxane (10 ml) at 100 °C for 16.

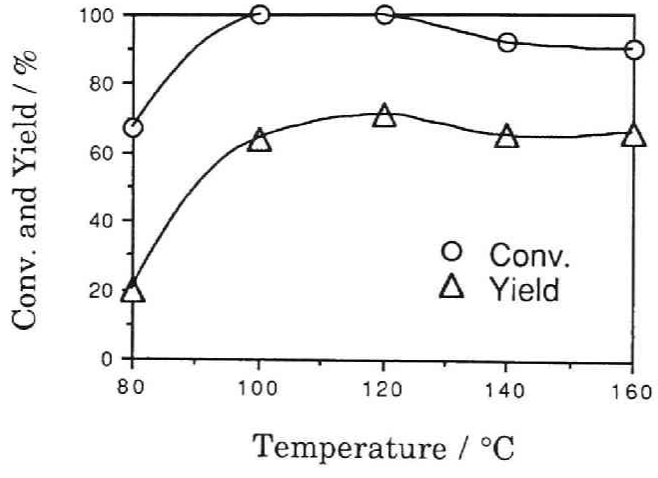


Figure 3. Effect of reaction temperature on palladium-catalyzed reductive *N*-heterocyclization of methyl *o*-nitrocinnamate.
Reaction conditions: methyl *o*-nitrocinnamate (2.0 mmol),$PdCl_2(PPh_3)_2$ (0.10 mmol), $SnCl_2$ (1,0 mmol), and 1,4-dioxane (10 ml) under CO (20 $kgcm^{-2}$) for 16.

As for the carbon monoxide pressure, the maximum yield of the indole reached 62% under 20 $kgcm^{-2}$. Both higher (up to 80 $kgcm^{-2}$) and lower (down to 5 $kgcm^{-2}$) carbon monoxide pressure led to low yield. Furthermore, the present reaction was examined under carbon monoxide atmosphere by means of a 50 ml Pyrex flask equipped with a reflux condenser and a 2L balloon. Under reflux in toluene (b.p. 110°C), the conversion and yield were 22% and 16%, respectively (Run 36 in Table V). Under reflux in diglyme (b.p. 162°C), the conversion and yield were 43% and 9%, respectively (Run 37 in Table V).

Table V. Effect of Solvents and Reaction Conditions on the Reductive *N*-Heterocyclization of Methyl *o*-Nitrocinnamate[a]

Run	Solvent	Temp./ °C	CO / $kgcm^{-2}$	Conv./%	Yield/%
1	1,4-dioxane	100	20	100	62
33	THF	100	20	97	38
34[b]	THF	100	20	64	26
35	toluene	100	20	60	36
36[b,c]	toluene	reflux(b.p.110°C)	1	22	16
37[c,d]	diglyme	reflux(b.p.162°C)	1	43	9
38	anisole	100	20	97	15

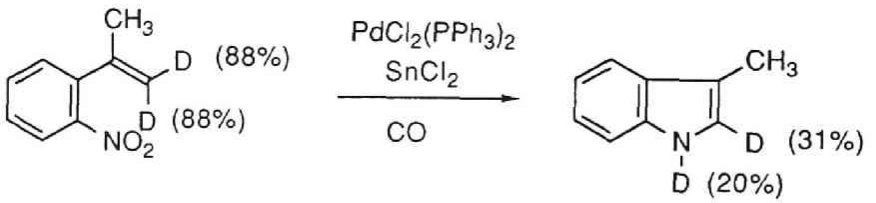
a) Methyl *o*-nitrocinnamate (2.0 mmol), $PdCl_2(PPh_3)_2$ (0.10 mmol), $SnCl_2$ (1.0 mmol), solvent (10 ml) for 16h. b) For 4 h. c) Used a 50 ml Pyrex flask with a reflux condenser and for a 2L balloon. d) For 6 h.

An effect of reaction temperature under 20 $kgcm^{-2}$ of initial carbon monoxide pressure was examined (Figure 3). At 120°C, the maximum yield of the indole reached 71%. Below 100°C, the conversion and yield reduced drastically. Above 140°C, the palladium catalyst was deposited as palladium metal during the reaction. On the basis of the optimization of the reaction conditions of methyl *o*-nitrocinnamate, methyl 2-indolecarboxylate was obtained in the best yield of 77% at 120°C under 20 $kgcm^{-2}$ of initial carbon monoxide pressure. The present reaction conditions are remarkably mild in

comparison with previously reported ruthenium carbonyl-catalyzed synthesis of indoles from *o*-nitrostyrene derivatives.[9]

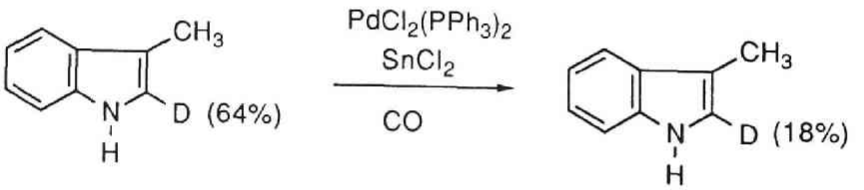
Mechanistic Study

In order to investigate the mechanism, β,β-dideuterio-α-methyl-*o*-nitrostyrene was prepared by Wittig reaction (see Experimental Section), and deuterium contents in the β-position were 88% respectively. *N*-Heterocyclization of this deuterium labeled *o*-nitrostyrene afforded 3-methylindole in which the deuterium content at 2-position of the generated indole was drastically reduced to 31% (eq 4). The 20% deuterium was also incorporated at 1-position. Even though the percentage of deuterium at 2-position was reduced, the result that 31% deuterium remains at 2-position suggests the possibility of the direct insertion of a nitrene intermediate to an olefinic β-C-H bond.



(4)

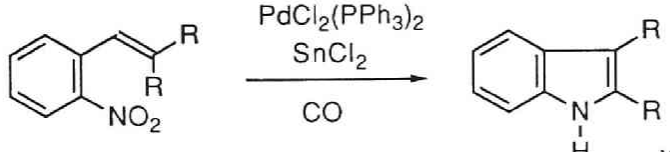
Furthermore, 3-methylindole labeled by deuterium at 2-position (64%) was separately prepared and treated under the present reaction conditions (eq 5). In the presence of both $PdCl_2(PPh_3)_2$ and $SnCl_2$, the deuterium percentage at 2-position was actually reduced to 18%.



(5)

Although, in the absence of both $PdCl_2(PPh_3)_2$ and $SnCl_2$, the deuterium of the 2-position did not exchange at all, in the presence of $PdCl_2(PPh_3)_2$ or $SnCl_2$, the deuterium percentage at the 2-position was reduced drastically. These deuterium labeled experiments suggest that the deuterium (hydrogen) on the 2-position of indole ring would easily exchange with the other hydrogens on the indole ring or hydrogens of solvent and triphenylphosphine ligand of palladium catalysts by orthometallation.

In addition, when β,β-dimethyl-*o*-nitrostyrene was employed in the present reductive *N*-heterocyclization, 2,3-dimethylindole was obtained in 52% yield (eq 6). Similarly, cyclopentylidene(*o*-nitrophenyl)methane was also transformed into 1,2,3,4-tetrahydrocarbazole in 45% yield via reductive *N*-heterocyclization and subsequent rearrangement of the alkyl group (eq 6).



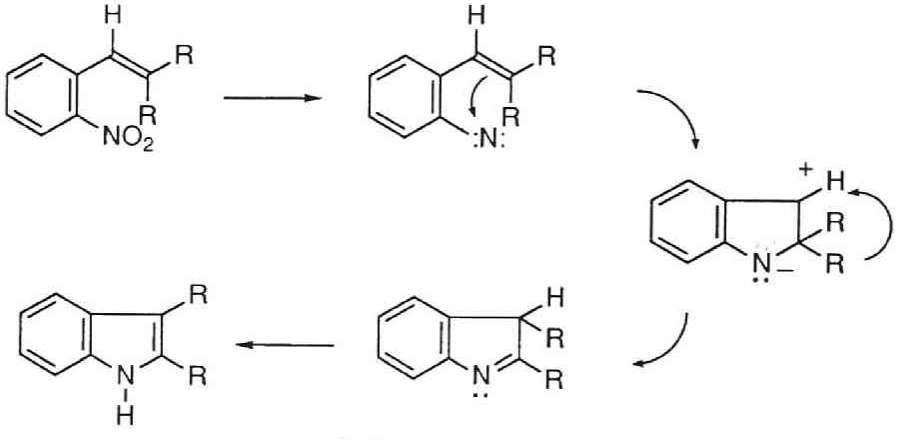
(6)

	yield
$R = CH_3$	52 %
$R,R = -(CH_2)_4-$	45 %

In these reactions, deoxygenation of the nitro group firstly proceeds to give the corresponding nitrene intermediate. The nitrene intermediate would electrophilically attack the olefinic carbon-carbon double bond, and subsequently, an alkyl group on β-position migrates to the α-position to stabilize the generated cationic carbon (α-position). Finally, a hydrogen transfer from 3-position (α-position) to 1-position of the constructed indole ring affords the corresponding 2,3-dialkylindoles. A similar migration of alkyl substituent has been reported by Sundberg in the synthesis of indole from β,β-disubstituted *o*-nitrostyrenes using an excess amount (3 equiv.) of triethyl phosphite as a reducing agent.[13] The proposed mechanism of the generation

of 2,3-disubstituted indoles from β,β-disubstituted *o*-nitrostyrenes is illustrated in Scheme 1.

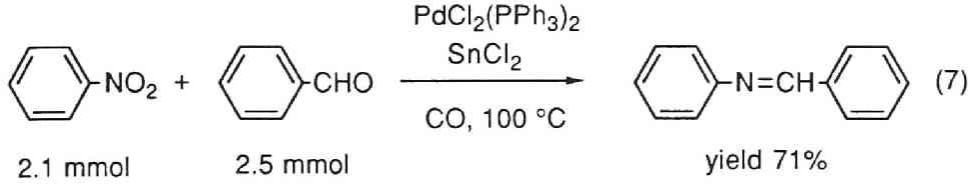
From the results mentioned above, the present reaction may also be rationalized by assuming a nitrene intermediate.[14] A plausible mechanism of the reductive *N*-heterocyclization of *o*-nitrostyrenes is illustrated in Scheme 2. Firstly, deoxygenation of the nitro group in *o*-nitrostyrene by carbon monoxide would occur to give the corresponding nitrene intermediate. This electrophilic nitrene[10] could attack the olefinic carbon, followed by a hydrogen transfer to give the corresponding indole.



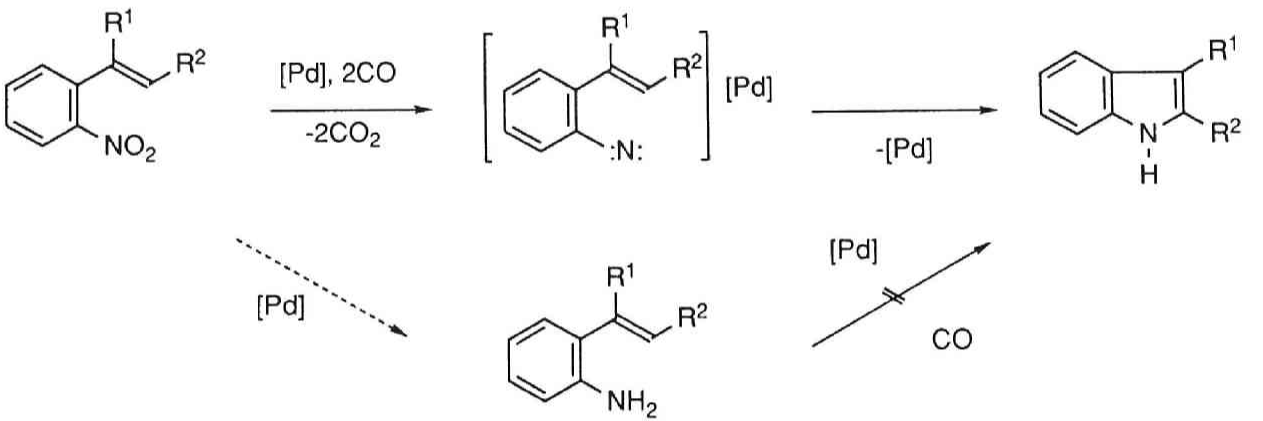
Scheme 1

In the case of *o*-nitrochalcone, since reductive coupling of the nitro group with the carbonyl group competed with the formation of the indole, both 2-benzoylindole (52%) and 2-phenylquinoline (34 %) were obtained as products (*vide supra*). Furthermore, in the case of *o*-nitrocinnamaldehyde, reductive coupling of the nitro group with the carbonyl group predominantly occurred to give only quinoline. Indeed, the present catalyst system ($PdCl_2(PPh_3)_2$ - $SnCl_2$) also promoted the reductive coupling of nitrobenzene with benzaldehyde to give *N*-benzylideneaniline in 71% yield (eq 7). The same reductive coupling

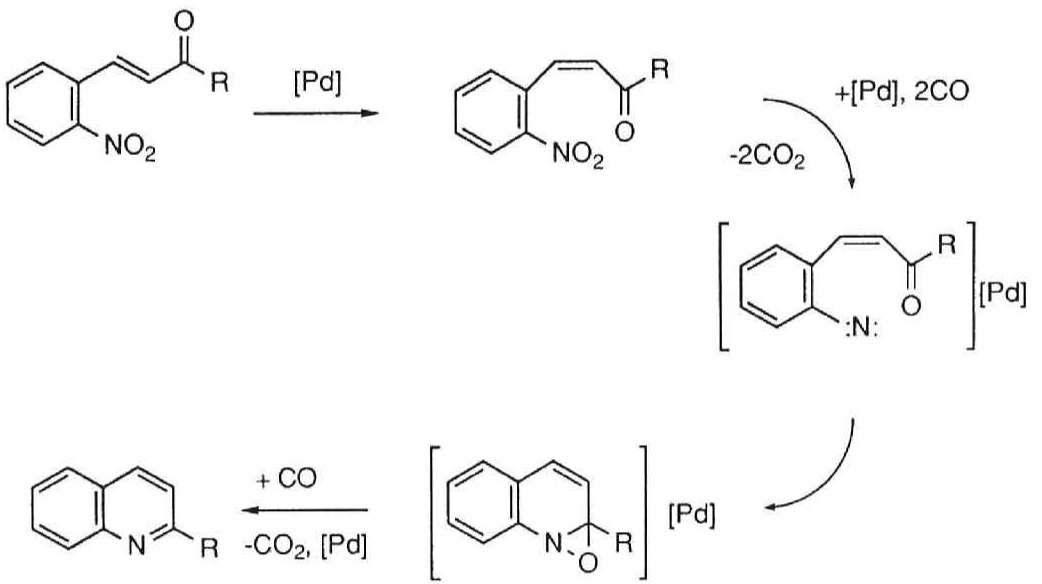
reaction catalyzed by rhodium carbonyl has already been reported by Iqbal, in which he also proposed the generation of a nitrene intermediate.[11]



A plausible route for the generation of quinoline derivatives is also illustrated in Scheme 3. The quinoline would be obtained by *intramolecular* reductive coupling of the nitro group with the carbonyl group, after *trans-cis* isomerization of olefinic carbon-carbon double bond.



Scheme 2



Scheme 3

[Experimental Section]

General materials.

The reagents employed in this study were dried and purified before use by the usual procedures. Carbon monoxide (> 99.9 %) was used without further purification. Transition-metal complexes, such as $PdCl_2(PPh_3)_2$,[15] $PdCl_2(PBu_3)_2$,[16] $PdCl_2$(dppe),[17] $PdCl_2$(bipy),[18] $PdCl_2(PhCN)_2$,[19] $Pd(PPh_3)_4$,[20] $PtCl_2(PPh_3)_2$,[21] $NiCl_2(PPh_3)_2$,[22] $RuCl_2(PPh_3)_3$,[23] and $RhCl(PPh_3)_3$,[24] were prepared by the literature's methods. $SnCl_2$, $SnBr_2$, and $AgBF_4$ were purchased from Aldrich Chemical Company and were used without further purification.

***o*-Nitrostyrene derivatives:** *o*-Nitrostyrene derivatives were prepared by the following procedure.

Methyl *o*-nitrocinnamate; The esterification of *o*-nitrocinnamic acid was performed with dimethyl sulfate according to the literature method.[25]

***o*-Nitrostyrene**; *o*-Nitrocinnamic acid was decarboxylated using copper powder in quinoline by the literature procedure.[26]

***o*-Nitrostilbene and β,β-Dimethyl-*o*-nitrostyrene;** They were prepared from *o*-nitrobenzylbromide with triethyl phosphite by Wittig-Houner reaction.[27]

***o*-Aminostilbene;** Reduction of *o*-nitrostilbene was performed with iron powder in acetic acid and ethanol.[7b]

α–Methyl-*o*-nitrostyrene; This compound was prepared by Wittig reaction.[28]

***o*-Nitrochalcone**; The condensation of *o*-nitrobenzaldehyde with acetophenone was carried out under basic conditions.[29]

Deuterium labeled substrates were prepared by the following methods.

β,β-Dideuterio-α-methyl-*o*-nitrostyrene; This compound was prepared by Wittig reaction of *o*-nitroacetopenone with (methyl-d_3)triphenylphosphonium iodide.[28]

2-Deuterio-3-methylindole; *N*-Benzensulfonyl-2-lithio-3-methylindole was prepared by the literature method,[30] and it was decomposed by the addition of deuterium oxide to give *N*-benzenesulfonyl-2-deuterio-3-methylindole. Subsequently, the sulfonyl substituent as a *N*-protecting group was removed by hydrolysis to afford the corresponding indole.[31]

General Procedures.

A mixture of *o*-nitrostyrene derivative (2.0 mmol), $PdCl_2(PPh_3)_2$ (0.10 mmol), $SnCl_2$ (1.0 mmol), and 1,4-dioxane (10 ml) was placed in a 50 ml stainless steel autoclave (Yuasa Giken; SUS 316) equipped with a glass liner and a magnetic stirring bar. The unit was sealed and then purged three times with 10 $kgcm^{-2}$ pressurization-depressurization cycles of carbon monoxide. The reactor was then pressurized to 20 $kgcm^{-2}$ with carbon monoxide (at room temperature), and heated to 100 °C within 10 min with stirring, and held at this temperature for 16 h. The reaction was terminated by rapid cooling, and gaseous products were discharged. The resulting brown solution was analyzed by GLC and FT-IR. The products were isolated by Kugelrohr distillation and/or medium pressure column chromatography (absorbent: silica gel; eluent: a mixture of hexane and ethyl acetate). The identification of the products was confirmed by FT-IR, ^{1}H- and ^{13}C-NMR, elemental analyses and GC-MS. The GLC analyses were carried out Shimadzu GC-8A chromatographs equipped with glass columns (3 mm i. d. x 3m) packed with Silicone OV-17 (2 % on Chromosorb W(AW-DMCS), 80-100 mesh), PEG-HT (5 % on Uniport HP, 60-80 mesh). The IR spectra were measured on a Shimadzu FTIR-8100 . The ^{1}H-NMR spectra were recorded at 90 MHz with a JEOL JNM FX-90 spectrometer and/or 270 MHz with a JEOL GSX-270 spectrometer. ^{13}C-NMR spectra were recorded at 25.05 MHz with JEOL JNM FX-100 spectrometer. Samples were dissolved in $CDCl_3$, and the

chemical shift values were expressed in relative to Me_4Si as an internal standard. Elemental analyses were performed at Microanalytical Center of Kyoto University. Mass spectra (MS) were obtained on a Shimadzu QP-2000 spectrometer. The spectral and analytical data of the products are shown below.

Methyl 2-indolecarboxylate: white solid; mp 148.0-148.4 °C; IR (KBr) 3400cm^{-1} (br, ν_{N-H}), 1694cm^{-1}(s, $\nu_{C=O}$): ^1H NMR($CDCl_3$, 270MHz) δ 3.95 (s, 3H, CH_3), 7.12-7.70(m, 5H, indole), 9.14(br, 1H, N*H*); ^{13}C NMR($CDCl_3$, 25.05MHz) δ 52.0(q, CH_3), 108.8(d, indole), 112.0(d, indole), 120.7(d, indole), 122.5(d, indole), 125.3(d, indole), 127.0(s, indole), 127.4(s, indole),137.0(s, indole) 162.7(s, *COO*); MS, m/z (relative intensity) 175(M^+, 52.1), 143(base-peak), 115(60.9), 89(34.0); Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 7.99. Found: C, 68.33; H, 5.17; N, 7.99.

2-Phenylindole: white solid; mp 187.8-188.5°C; ^1H NMR($CDCl_3$, 270MHz) δ 6.81(s, 1H, indole), 7.08-7.65(m, 9H, phenyl and indole), 8.28(br, 1H, N*H*); ^{13}C NMR($CDCl_3$, 25.05MHz) δ 99.6(d, indoleC3),110.6(d, indoleC7), 119.9(d, indoleC6), 120.3(d, indoleC4), 122.0(d, indoleC5), 124.8(d, phenylC3), 127.4(d, phenylC4), 128.7(d, phenylC2), 128.9(s, indoleC9), 132.0(s, phenylC1), 136.4(s, indoleC2), 137.4(s, indoleC8); MS, m/z (relative intensity) 193(M^+, base-peak), 165(20.3), 96(20.5) ; Anal. Calcd for $C_{14}H_{11}N$: C, 87.01; H, 5.74; N, 7.25. Found: C, 87.25; H, 5.57; N, 7.05.

2-Benzoylindole: white solid; mp 152.2-153.0 °C; IR (KBr) 3400cm^{-1}(br, ν_{N-H}), 1624 cm^{-1}(s, $\nu_{C=O}$); ^1H NMR($CDCl_3$, 270MHz) δ 7.05-8.07(m,11H, indole and phenyl); ^{13}C NMR($CDCl_3$, 25.05MHz) δ 112.4(d), 113.0(d), 120.9(d), 123.1(d), 126.4(d), 127.6(s), 128.3(d), 129.2(d), 132.2(d), 134.3(s), 137.8(s), 138.0(s), 187.3(s, *CO*); MS, m/z (relative intensity) 221(M^+, base-peak), 220(M^+-1, 44.6), 204(22.9),

144(39.1), 89(42.4), 77(47.2); Anal. Calcd for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.58; H, 4.98; N, 6.26.

2-Phenylquinoline: white solid; mp 82.0-82.5°C; ^1H NMR($CDCl_3$, 270MHz) δ 7.43-7.53(m, 4H), 7.66-7.82(m, 3H), 8.11-8.19(m, 4H); ^{13}C NMR($CDCl_3$, 67.8MHz) δ 118.93(d, quinolineC3), 126.22(d, quinolineC6), 127.14(s, quinolineC4a), 172.42(d, quinolineC5), 127.54(s, phenyl), 128.79(d, phenyl), 129.29(d, phenyl), 129.60(d, quinolineC7), 129.73(d, quinolineC8), 136.69(d, quinolineC4), 139.65(s, phenyl), 148.26(s, quinolineC8a), 157.29(s, quinolineC2); MS, m/z (relative intensity) 205(M^+, base-peak), 204(M^+-1, 95.2), 104(29.7); Anal. Calcd for $C_{15}H_{11}N$: C, 87.78; H, 5.40; N, 6.82. Found: C, 87.83; H, 5.16; N, 6.82.

Quinoline: bp 150 °C/ 17 mmHg(Kugelrohr distillation); ^1H NMR($CDCl_3$, 270MHz) δ 7.25-7.83(m, 4H), 8.02-8.18(m, 2H), 8.91(d, 1H); ^{13}C NMR($CDCl_3$, 25.05MHz) δ 121.0(d, C2), 126.6(d, C5), 127.7(d, C4), 128.3(s, C8), 129.2(d, C7), 129.6(d, C6), 136.3(d, C3), 147.9(s, C9), 150(d, C1); MS, m/z (relative intensity) 129(M^+, base-peak), 102(29.8), 51(31.1).

3-Methylindole: white solid; mp 92.5-93.4 °C; ^1H NMR($CDCl_3$, 270MHz) δ 2.30(s, 3H, CH_3), 6.79(d, 1H, indole, J=1.0Hz), 7.07-7.21(m, 3H, indole), 5.54(br, 1H, N*H*), 7.56(d, 1H, indole) ; ^{13}C NMR($CDCl_3$, 25.05MHz) δ 9.6(q, CH_3), 100.9(d, C7), 111.4(s, C3), 118.7(d, C4), 119.0(d, C6), 121.5(d), 121.7(d), 128.1(s, C9), 136.1(s, C8); MS, m/z (relative intensity) 131(M^+, 63.4), 130(M^+-1, base-peak); Anal. Calcd for C_9H_9N: C, 82.41; H, 6.91; N, 10.68. Found: C, 82.45; H, 6.98; N, 10.52.

***N,N*-Diethyl 2-indolecarbamide**: white solid; mp 163.2-164.5°C; IR (KBr) 3400cm^{-1} (br, ν_{N-H}), 1607cm^{-1}(s, $\nu_{C=O}$); ^1H NMR($CDCl_3$, 270MHz) δ 1.35(br, 6H,

CH_3), 3.70(br, 4H, -CH_2-), 6.81(d, 1H, indoleC3-H, J=2.0Hz), 7.11(ddd, 1H, indoleH, J=8.1, 7.1, 1.2 Hz), 7.26(ddd, 1H, indoleH, J=8.3, 7.1, 1.2Hz), 7.45(d, 1H, indoleH, J=8.3Hz), 7.65(d, 1H, indoleH, J=8.1Hz), 9.99(br, 1H, N*H*); ^{13}C NMR($CDCl_3$, 67.8MHz) δ 13.62(br, -CH_3), 42.32(br, -CH_2-), 104.29(d, indoleC), 111.81(d, indoleC), 120.27(d, indoleC), 121.82(d, indoleC), 124.13(d, indoleC), 127.89(d, indoleC), 135.06(s, indoleC), 135.59(s, indoleC), 162.36(s, *C*O); MS, m/z (relative intensity) 216(M^+, 37.9), 144(base-peak), 117(24.2), 89(45.9), 72(73.2).

2,3-Dimethylindole: white solid; bp 170 °C / 0.6 mHg(Kugelrohr distillation); ^{1}H NMR($CDCl_3$, 270MHz) δ 2.20(s, 3H, -CH_3), 2.27(s, 3H, -CH_3), 7.05-7.47(m, 4H, indole), 7.61(br, 1H, N*H*) ; ^{13}C NMR($CDCl_3$, 25.05MHz) δ 8.4(q, -CH_3), 11.5(q, -CH_3), 105.6(s,C3),109.5(d, C7),117.8(d, C4), 119.2(d, C6), 120.7(d, C5), 129.7(s, C3a),131.1(s, C2), 134.0(s, C7a) ; MS, m/z (relative intensity) 145(M^+, 84.1), 144(M^+-1, base-peak), 130(M^+-CH_3, 42.1).

1,2,3,4-Tetrahydrocarbazole: white solid; mp 114-117 °C; ^{1}H NMR($CDCl_3$, 270MHz) δ 1.83-1.90(m, 4H, -CH_2-), 2.64-2.71(m, 4H, -CH_2-), 7.03-7.46(m, 4H, indole), 7.50(br, 1H, N*H*); ^{13}C NMR($CDCl_3$, 67.80MHz) δ 20.86(-CH_2-), 23.15(2-CH_2-), 23.24(-CH_2-), 110.04(C4a), 110.30(C8), 117.65(C5), 119.01(C7), 120.90(C6), 127.74(C4b), 134.04(C9a), 135.56(C8a); MS, m/z (relative intensity) 171(M^+, 62.2), 143(M^+-2CH_2, base-peak).

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Chapter 3

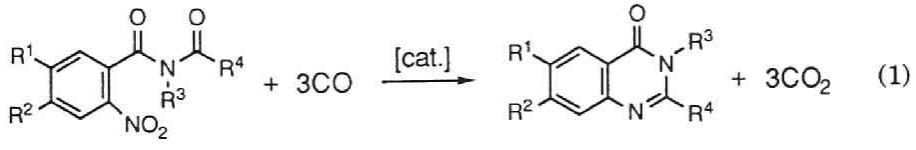
Transition-Metal Complex-Catalyzed Reductive *N*-Heterocyclization: Synthesis of 4(3*H*)-Quinazolinone Derivatives from *N*-(2-Nitrobenzoyl)amides

[Summary]

Several transition-metal complexes, especially $Ru_3(CO)_{12}$ and $Pt(PPh_3)_4$, smoothly catalyze the reductive *N*-heterocyclization of *N*-(2-nitrobenzoyl)amides to afford the corresponding 4(3*H*)-quinazolinone derivatives in 68-94% yields. The present reaction can be applied to the facile synthesis of indolo[2,1-*b*]quinazoline-6,12-dione, which is well-known as antibiotic tryptanthrine. This alkaloid was successfully synthesized by the reductive *N*-heterocyclization of *N*-(2-nitrobenzoyl)isatine in 48% yield. On the other hand, when an excess amount of, *i.e.*, three equivalent of pentacarbonyliron ($Fe(CO)_5$) was employed in the reaction of *N*-(2-nitrobenzoyl)-2-azacycloheptanone, the corresponding 4(3*H*)-quinazolinone was obtained in 51% yield under an argon atmosphere. The present reaction can be rationalized by assuming a transition-metal nitrene intermediate, which seems to be generated by the deoxygenative reduction of the nitro group in *N*-(2-nitrobenzoyl)amide by carbon monoxide.

[Introduction]

The effective use of transition-metal complexes for synthesis of various heterocyclic ring systems has been enormously developed in recent years,[1] and we have also been studying *N*-heterocyclization reaction catalyzed by transition-metal complexes, especially ruthenium complexes, with a final object to developing them to the point where they can be regarded as a routine and general synthesis.[2] Among the various possible methods for the synthesis of *N*-heterocyclic compounds, we are recently interested in transition-metal complex-catalyzed reductive *N*-heterocyclization of nitro compounds via an active transition-metal nitrene intermediate.[3] In this chapter, we report a first ruthenium-catalyzed synthesis of 4(3*H*)-quinazolinone derivatives by the reductive *N*-heterocyclization of *N*-(2-nitrobenzoyl)amides under carbon monoxide pressure (eq 1). Many of quinazolinone alkaloids such as tryptanthrine,[4a] vasicinone,[4b] anisotine,[4c] and rutaecarpine[4d] are important because of their biological activities. However, the catalytic synthesis of these compounds was extremely limited.[5]



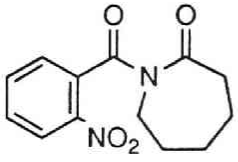
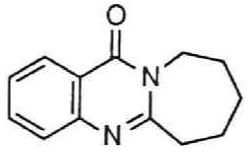
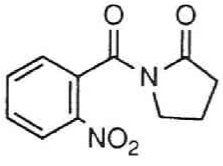
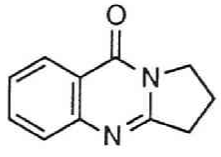
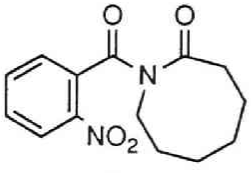
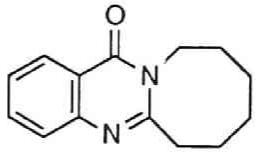
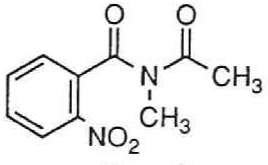
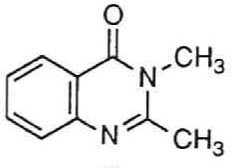
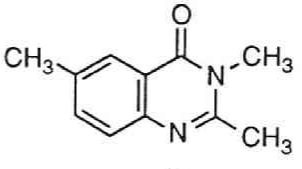
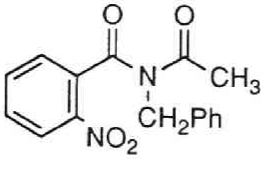
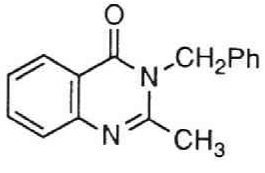
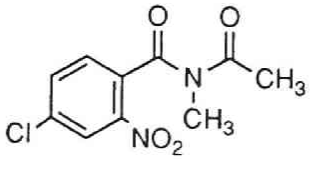
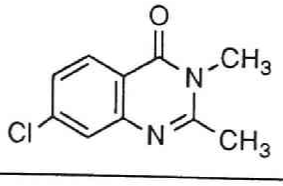
(1)

[cat.] = $Ru_3(CO)_{12}$, $Pt(PPh_3)_4$ etc.

[Results and discussion]

Representative results of the synthesis of 4(3*H*)-quinazolinone derivatives from *N*-(2-nitrobenzoyl)amides using $Ru_3(CO)_{12}$ as a catalyst are summarized in Table I.

Table I. Synthesis of 4(3*H*)-Quinazolinone Derivatives from *N*-(2-Nitrobenzoyl)amides in the Presence of $Ru_3(CO)_{12}$ Catalyst[a]

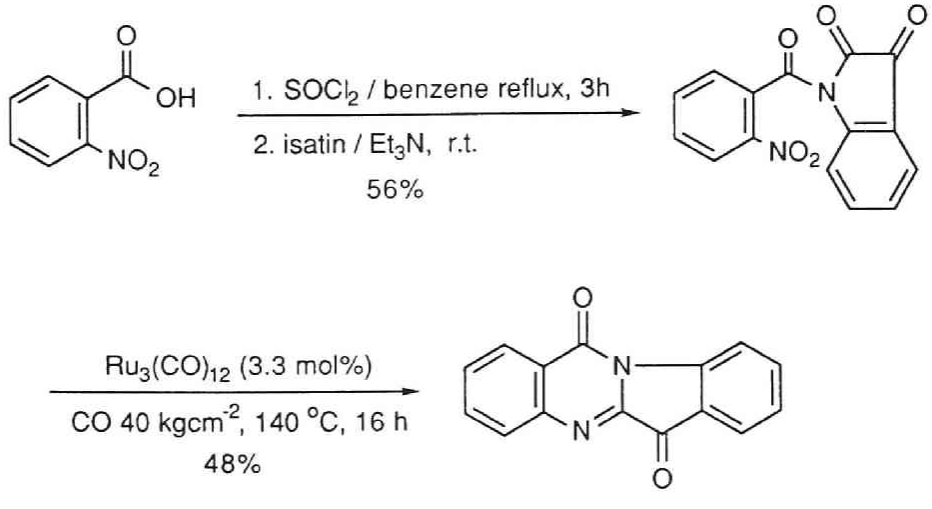
Run	Substrate	Product	Yield/%[b]
1			88 (92)
2[c]			68
3			94
4			93
5			92
6			88
7			77

a) *N*-(2-Nitrobenzoyl)amides (2.0 mmol), 1,4-dioxane (10 ml), $Ru_3(CO)_{12}$ (0.067 mmol) under CO (40 $kgcm^{-2}$) at 140 °C for 16 h. b) Isolated yields (GLC yield). c) At 160 °C.

N-(2-Nitrobenzoyl)amides were smoothly transformed into the corresponding 4(3*H*)-quinazolinone derivatives in 68-94% yield. The quinazolinones obtained in this reaction are versatile intermediates for the synthesis of quinazolinone alkaloids. For example, total synthesis of vasicinone via azacyclopentano[2,1-*b*]-4(3*H*)-quinazolinone, the product in run 2, has already been reported by Onaka et al.,[6] and the improved method was afterward reported by Mori et al.[5]

The present reaction can be applied to the facile synthesis of indolo[2,1-*b*]-quinazoline-6,12-dione, which is an antibiotic tryptanthrine.[4a,b,c] As shown in Scheme 1, indolo[2,1-*b*]quinazoline-6,12-dione was obtained in 48% yield by the present reductive *N*-heterocyclization of *N*-(2-nitrobenzoyl)isatin which was easily prepared from 2-nitrobenzoic acid and isatin.

Scheme 1



The catalytic activities of several transition-metal complexes were examined in the reductive *N*-heterocyclization of *N*-(2-nitrobenzoyl)-2-azacycloheptanone (Table II). Zerovalent ruthenium and platinum complexes generally showed high catalytic activities (Runs 8, 9, 12 and 13). Although the catalytic activities of divalent $RuCl_2(PPh_3)_3$ and $PtCl_2(PPh_3)_2$ complexes were

low (Runs 10 and 14), the addition of appropriate base such as K_2CO_3 or pyridine drastically improved the catalytic activity of these complexes (Runs 11 and 15). Phosphine ligands did not affect the present reaction. However, the catalytic activities of other group VII and VIII metal complexes including palladium complexes, which effectively catalyzed the reductive *N*-heterocyclization of *N*-(2-nitrobenzylidene)amines to 2*H*-indazoles[3a] and *o*-nitrostyrenes to indoles,[3b] were quite low.

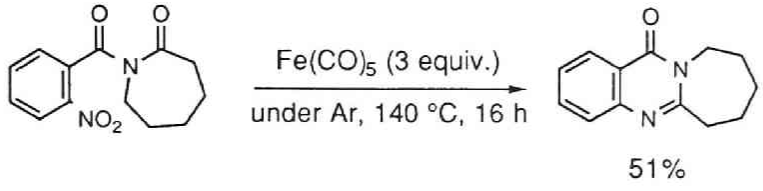
Table II. Catalytic Activities of Several Transition-Metal Complexes for the Reductive *N*-Heterocyclization of *N*-(2-Nitrobenzoyl)-2-azacycloheptanone[a]

Run	Catalyst /mmol	Additive	Conv./%[b]	Yield/%[b]
8	$Ru_3(CO)_{12}$ (0.034)	-	63	60
9	$Ru(CO)_3(PPh_3)_2$ (0.10)		64	45
10	$RuCl_2(PPh_3)_3$ (0.10)		10	9
11	$RuCl_2(PPh_3)_3$ (0.10)	K_2CO_3[c]	100	67
12	$Pt(PPh_3)_4$ (0.10)	-	81	76
13	$Pt(CO)_2(PPh_3)_2$ (0.10)		69	65
14	$PtCl_2(PPh_3)_2$ (0.10)		22	17
15	$PtCl_2(PPh_3)_2$ (0.10)	Pyridine[d]	65	60
16	$Pd(PPh_3)_4$ (0.10)		34	31
17	$Pd(CO)(PPh_3)_3$ (0.10)	-	23	19
18	$PdCl_2(PPh_3)_2$ (0.10)	$SnCl_2$[e]	71	13
19	$Fe_3(CO)_{12}$ (0.034)	-	14	8
20	$Co_2(CO)_8$ (0.050)	-	9	5
21	$Rh_6(CO)_{16}$ (0.017)		6	4
22	$Mn_2(CO)_{10}$ (0.050)		14	4

a) *N*-(2-Nitrobenzoyl)-2-azacycloheptanone (2.0 mmol), 1,4-dioxane (10 ml) under CO (20 $kgcm^{-2}$) at 120 °C for 16 h. b) Determined by GLC. c) 3.0 mmol. d) 1.0 ml (12.4 mmol). e) 1.0 mmol.

Furthermore, when an excess amount of, *i.e.*, three equivalent of pentacarbonyliron ($Fe(CO)_5$) instead of a catalytic amount of $Ru_3(CO)_{12}$ was employed in the reaction of *N*-(2-nitrobenzoyl)-2-azacycloheptanone, azacycloheptano[2,1-*b*]-4(3*H*)-quinazolinone was actually obtained in 51% yield

under an argon atmosphere (eq 2). This result suggests that carbon monoxide pressure is not always essential for the present reaction, if an enough amount of transition-metal carbonyl complexes is employed.



51% (2)

The present reaction can be rationalized by assuming a transition-metal nitrene intermediate.[7] Firstly, deoxygenative reduction of the nitro group in *N*-(2-nitrobenzoyl)amide by carbon monoxide would proceed to give an active nitrene intermediate.[8] It is well-known that nucleophilic nitrene complexes commonly react with the carbonyl groups in aldehydes or ketones to yield the corresponding imines.[9] For example, Nugent has reported that the reaction of $(Me_3SiO)_2Cr(N^tBu)_2$ with benzaldehyde gives a monooxo complex, $(Me_3SiO)_2CrO(N^tBu)$, together with the Schiff base, benzylidene-*tert*-butylamine.[10b] In the present reaction, the *intramolecular metathesis-like* reaction of the generated nitrene complex with carbonyl group would proceed in a similar manner to give the corresponding quinazolinone and transition-metal oxo complex. The oxo complex can be reduced to zerovalent active carbonyl complex by carbon monoxide[11] and the catalytic cycle is regenerated. After the reductive *N*-heterocyclization of *N*-(2-nitrobenzoyl)-2-azacycloheptanone (Run 1), carbon dioxide was generated and detected in a gas phase in 241% yield based on the nitro compound. This result was also coherently explained by the above-mentioned mechanism.※

In conclusion, transition-metal complex-catalyzed reductive N-heterocyclization reaction provides a novel and elegant synthetic method for 4(3*H*)-quinazolinone derivatives from *N*-(2-nitrobenzoyl)amides. Works are now in progress to provide definitive mechanistic information and to apply this series

of reductive *N*-heterocyclization reactions[3] to the construction of other heterocyclic ring systems.

[Experimental Section]

Materials.

The reagents employed in this study were dried and purified before use by the usual procedures. Carbon monoxide (>99.9%) were used without further purification. $Ru(CO)_3(PPh_3)_2$,[13] $RuCl_2(PPh_3)_3$,[14] $Pt(PPh_3)_4$,[15] $Pt(CO)_2(PPh_3)_2$,[16] $PtCl_2(PPh_3)_2$,[17] $Pd(PPh_3)_4$,[18] $Pd(CO)(PPh_3)_3$[19], $PdCl_2(PPh_3)_2$[20] and $Rh_6(CO)_{16}$[21] were prepared by the literature's methods. $Ru_3(CO)_{12}$, $Fe_3(CO)_{12}$ and $Mn_2(CO)_{10}$ were purchased from Strem Chemicals and $Co_2(CO)_8$ was purchased from Mitsuwa Chemicals and used without further purification.

General Procedures.

A mixture of *N*-(2-nitrobenzoyl)amide (2.0 mmol), $Ru_3(CO)_{12}$ (0.067 mmol), and dry 1,4-dioxane (10 ml) was placed in a stainless steel autoclave (Yuasa Giken SUS 316) equipped with a glass liner and a magnetic stirring bar. The unit was sealed and purged of air by pressurization with carbon monoxide to 10 $kgcm^{-2}$, and depressurization to an atmospheric pressure. This pressurization-depressurization cycle was repeated twice. The reactor was then again pressurized to 40 $kgcm^{-2}$ with carbon monoxide at room temperature, and was heated to 140 °C over 10 min with stirring. The stirred mixture was held at this temperature for 16 h. The reaction was then quenched by rapid cooling, and the gaseous products were allowed to escape. The resulted brown solution was analyzed by GLC and FT-IR. The products were isolated by Kugelrohr distillation.

Analytical Procedures.

The products were identified by FT-IR, ^{1}H- and ^{13}C-NMR, elemental analysis and GC-MS. The GLC analyses were carried out on a Shimadzu GC-8A chromatograph equipped with a glass column (2.6 mm i.d. × 3 m) packed with Silicone OV-17 (2% on Chromosorb W (AW-DMCS), 80-100 mesh). ^{1}H-NMR spectra were recorded at 270 MHz and ^{13}C-NMR spectra were recorded at 67.80 MHz in $CDCl_3$ or DMSO-d_6 with a JEOL GSX-270. Elemental analyses were performed at the Microanalytical Center of Kyoto University.

Azacycloheptano[2,1-*b*]-4(3*H*)-quinazolinone[22]**:** white solid; mp 95.1-96.8 °C; IR(KBr) 1655, 1611, 1592, 1478 cm^{-1}; ^{1}H-NMR($CDCl_3$, 270 MHz) δ 1.84(br, 6H, -(CH_2)$_3$-), 3.06(br, 2H, -CH_2-), 4.38(br, 2H, -CH_2N-), 7.42(ddd, 1H, H-6, *J*=1.7, 7.1, 8.1 Hz), 7.60(ddd, 1H, H-8, *J*=0.5, 1.7, 8.3 Hz), 7.70(ddd, 1H, H-7, *J*=1.5, 7.1, 8.3 Hz), 8.25(ddd, 1H, H-5, *J*=0.5, 1.5, 8.1 Hz); ^{13}C-NMR($CDCl_3$, 67.80 MHz) δ 25.4, 28.0 and 29.5(t, -CH_2-), 37.6(t, -N=CCH_2-), 42.7(t, -NCH_2-), 119.9(s, C-10), 126.0(d, C-8), 126.4(d, C-6), 126.7(d, C-5), 133.8(d, C-7), 147.1(s, C-9), 159.3(s, C-2), 161.5(s,, C-4); mass spectrum (electron impact) *m*/*z* 214(M^+, base peak), 213(M^+-1, 48.6%), 199(39.2%), 185(77.8%), 160(51.2%). Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.61; H, 6.57; N, 12.96.

Azacyclopentano[2,1-*b*]-4(3*H*)-quinazolinone: white solid; mp 107.6-108.7°C; IR(KBr) 1678, 1622, 1466 cm^{-1}; ^{1}H-NMR($CDCl_3$, 270 MHz) δ 2.26(tt, 2H, -CH_2C*H*$_2CH_2$-, *J*=6.9, 7.9 Hz), 3.14(t, 2H, -N=CC*H*$_2CH_2$-, *J*= 7.9 Hz), 4.17(t, 2H, NC*H*$_2CH_2$-, *J*=6.9 Hz), 7.41(ddd, 1H, H-6, *J*=1.0, 6.9, 8.4 Hz), 7.59(dd, 1H, H-8, *J*=1.0, 7.9 Hz), 7.69(ddd, 1H, H-7, *J*=1.5, 6.9, 7.9 Hz), 8.23(dd, 1H, H-5, *J*=1.5, 8.4Hz); ^{13}C-NMR($CDCl_3$, 67.80 MHz) δ 19.4(t,-$CH_2CH_2CH_2$-), 32.3(t, -N=CCH_2-), 46.3(t, -NCH_2-), 120.1(s, C-10), 125.8(d, C-8), 125.9(d, C-6), 126.3(d, C-5), 133.7(d, C-7), 148.6(s, C-9), 159.0(s, C-2), 160.4(s, C-4); mass spectrum (electron impact) *m*/*z*

186(M^+, 75.8%), 185(M^+-1, base peak). Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.05. Found: C, 70.67; H, 5.36; N, 15.00.

Azacyclooctano[2,1-*b*]-4(3*H*)-quinazolinone[22]: white solid; mp 110.0-110.6°C; IR(KBr) 1680, 1609, 1586cm^{-1}; ^{1}H-NMR($CDCl_3$, 270 MHz) δ 1.41-1.42(m, 2H, -C*H*$_2$-), 1.56-1.62(m, 2H, -C*H*$_2$-),1.84-2.00(m, 4H, -(C*H*$_2$)$_2$-), 2.99-3.03(m, 2H, -N=CC*H*$_2$-), 4.31(br, 2H, -NC*H*$_2$-), 7.41(ddd, 1H, H-6, *J*=1.5, 6.9, 7.9Hz), 7.62(dd, 1H, H-8, *J*=1.5, 8.4Hz), 7.70(ddd, 1H, H-7, *J*=1.5, 6.9, 8.4Hz), 8.24(dd, 1H, H-5, *J*=1.5, 7.9Hz); ^{13}C-NMR($CDCl_3$, 67.80 MHz) δ 24.3, 26.1, 28.7, 30.7, 35.5(t, -*C*H$_2$-) 43.0(t, -N*C*H$_2$-), 120.4(s, C-10), 126.1(d, C-8), 126.6(d, C-5), 126.6(d, C-6), 133.9(d, C-7), 147.8(s, C-9), 159(s, C-2), 161.7(s, C-4); mass spectrum (electron impact) *m*/*z* 228(M^+, base peak), 213(M^+-1, 32.9%), 199(39.2%),185(41.0%) 174(30.7%), 160(93.1%). Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.65; H, 7.12; N, 12.27.

2,3-Dimethyl-4(3*H*)-quinazolinone: white solid; mp 109.0-109.5°C; IR(KBr) 1671, 1607, 1474cm^{-1}; ^{1}H-NMR($CDCl_3$, 270 MHz) δ 2.62(s, 3H, -C*H*$_3$), 3.62(s, 3H, NC*H*$_3$), 7.43(ddd, 1H, H-6, *J*=1.2, 7.1, 8.1Hz), 7.60(ddd, 1H,H-8, *J*=0.5, 1.2, 8.3Hz), 7.71(ddd, 1H, H-7, *J*=1.5, 7.1, 8.3Hz), 8.25(ddd, 1H, H-5, *J*=0.5, 1.5, 8.1Hz); ^{13}C-NMR($CDCl_3$, 67.80 MHz) δ 23.5(q, -*C*H$_3$), 30.9(q, -N*C*H$_3$), 119.8(s, C-10), 126.0(d, C-8), 126.2(d, C-6), 126.3(d, C-5), 133.7(d, C-7), 146.8(s, C-9), 154.0(s, C-2), 161.7(s, C-4); mass spectrum (electron impact) *m*/*z* 174(M^+, base peak), 159(M^+-Me, 57.1%), 146(29.5%), 56(78.8%). Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.77; H, 5,68; N, 16.07.

2,3,6-Trimethyl-4(3*H*)-quinazolinone: white solid; mp 104.6-105.9°C; IR(KBr) 1667, 1601, 1495cm^{-1}; ^{1}H-NMR($CDCl_3$, 270 MHz) δ 2.43(s, 3H, -C*H*$_3$), 2.54(s, 3H, -C*H*$_3$), 3.54(s, 3H, -NC*H*$_3$), 742-74.9(m, 2H, H-7 and H-8) 7.95(d, 1H, H-5, *J*=1.0Hz); ^{13}C-NMR($CDCl_3$, 67.80 MHz) δ 21.2(q, -*C*H$_3$), 23.4(q, -*C*H$_3$), 30.8(q, -N*C*H$_3$),

119.8(s, C-10), 125.9(d, C-8), 126.2(d, C-5), 135.4(d, C-7), 136.2(s, C-6), 145.1(s, C-9), 153.5(s, C-2), 161.9(s, C-4); mass spectrum (electron impact) m/z 188(M^+, base peak), 173(47.7%), 160(26.2%), 56(80.5%). Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.16; H, 6.42; N, 14.81.

7-Chloro-2,3-dimethyl-4(3*H*)-quinazolinone: white solid; mp 167.2-168.0°C; IR(KBr) 1667, 1601, 1495cm^{-1}; ^{1}H-NMR($CDCl_3$, 270 MHz) δ 2.59(s, 3H, -CH_3), 3.58(s, 3H, -NCH_3), 7.34(dd, 1H, H-6, J=2.0, 8.4Hz), 7.55(d, 1H, H-8, J=2.0Hz), 8.11(d, 1H, H-5, J=8.4Hz); ^{13}C-NMR($CDCl_3$, 67.80 MHz) δ 23.5(s, -CH_3), 31.0(s, NCH_3), 118.6(s, C-10), 126.2(d, C-8), 126.8(d, C-6), 128.2(d, C-5), 140.1(s, C-7), 148.1(s, C-9), 155.7(s, C-2), 161.5(s, C-4); mass spectrum (electron impact) m/z 210(M[^{37}Cl]$^+$, 32.2%), 208(M[^{35}Cl]$^+$, base peak), 193(53.2%), 180(28.4%), 56(97.9%). Anal. Calcd for $C_{10}H_9N_2OCl$: C, 57.57; H, 4.35; N, 13.42. Found: C, 57.56; H, 4.19; N, 13.42.

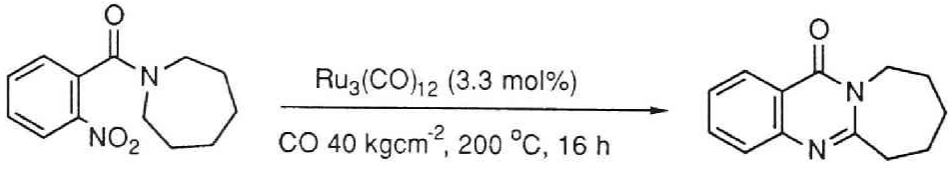
3-Benzyl-2-methyl-4(3*H*)-quinazolinone: white solid; mp 51.5-52.9°C; IR(KBr) 1676, 1599, 1476cm^{-1}; ^{1}H-NMR($CDCl_3$, 270 MHz) d 2.53(s, 3H, -CH_3), 5.38(s, 2H, -NCH_2Ph), 7.17-7.31(m, 5H, phenyl), 7.43(ddd, 1H, H-6, J=1.2, 7.1, 8.1Hz), 7.63(ddd, 1H, H-8, J=0.5, 1.2, 8.3Hz), 7.73(ddd, 1H, H-7, J=1.5, 7.1, 8.30(ddd, 1H, H-5, J=0.5, 1.5, 8.1Hz); ^{13}C-NMR($CDCl_3$, 67.80 MHz) δ 23.3(q, -CH_3), 47.1(t, NCH_2Ph), 120.3(s, C-10), 126.4(d, C-8 and phenyl 2, 6), 126.6(d, C-6), 126.9(d, C-5), 127.6(d, phenyl 4), 128.8(d, phenyl 3, 5), 134.3(d, C-7), 135.8(s, phenyl 1), 147.3(s, C-9), 154.5(s, C-2), 152.2(s, C-4); mass spectrum (electron impact) m/z 250(M^+, 52.3%), 249(M^+-1, 19.8%), 235(M^+-Me, 12.6%), 144(M^+-(Me+Bz), 22.6%), 91(Bz^+, base peak). Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.95; H, 5.61; N, 11.08.

Indolo[2,1-*b*]quinaozline-6,12-dione: yellow solid; mp 265.5-267.0°C; IR(KBr) 1728, 1692, 1316cm^{-1}; ^{1}H-NMR(DMSO-d_6, 270 MHz) δ 7.35(dd, 1H, H-8 J=7.4, 7.4Hz),

7.60(dd, 1H, H-2, J=7.4, 1.0Hz), 7.71(m, 1H, H-9), 7.78(m, 1H, H-3), 7.84(dm, 1H, H-7, J=7.9Hz), 7.96(dm, 1H, H-4, J=7.9Hz), 8.36(dd, 1H, H-1, J=7.9, 1.5Hz), 8.55(dm, 1H, H-10, J=8.4Hz); ^{13}C-NMR(DMSO-d_6, 67.80 MHz) δ 116.92(d), 122.13(s), 123.20(s), 124.61(d), 126.79(d), 126.84(d), 129.74(d), 129.80(d), 135.06(d), 137.64(d), 144.93(s),145.88(s), 146.35(s), 157.61(s), 182.35(s); mass spectrum (electron impact) m/z 248(M^+, base peak), 220(42.6%), 192(29.3%), 165(10.8%). Anal. Calcd for $C_{15}H_8N_2O_2$: C, 72.58; H, 3.25; N, 11.28. Found: C, 72.28; H, 3.41; N, 11.17.

[Footnote]

*The reductive *N*-heterocyclization of *N*-(2-nitrobenzoyl)azacycloheptane, which has no carbonyl group, afforded the corresponding azacycloheptano[2,1-*b*]-4(3*H*)-quinazolinone ($Ru_3(CO)_{12}$ catalyst at 200 °C for 16 h under 40 kgcm^{-2} of CO), although the yield of the product was only 9% (eq 3). This result also suggests the generation of an active nitrene intermediate which can insert into a saturated C-H bond,[12] and excludes that the reaction proceeds via the corresponding *N*-(2-aminobenzoyl)amide.



(3)

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Chapter 4

Palladium Complex-Catalyzed Reductive *N*-Heterocyclization of 2-Nitrobenzaldehydes or 2-Nitrophenyl Ketones with Formamide into Quinazoline Derivatives

[Summary]

A combination of palladium complex ($PdCl_2(PPh_3)_2$) with molybdenum (V) chloride shows a high catalytic activity for the intermolecular reductive *N*-heterocyclization of 2-nitrobenzaldehydes or 2-nitrophenyl ketones with formamide to give the corresponding quinazoline derivatives in moderate yields. For example, by the reaction of 2-nitrobenzaldehyde with formamide, quinazoline was obtained in 46% yield.

[Introduction]

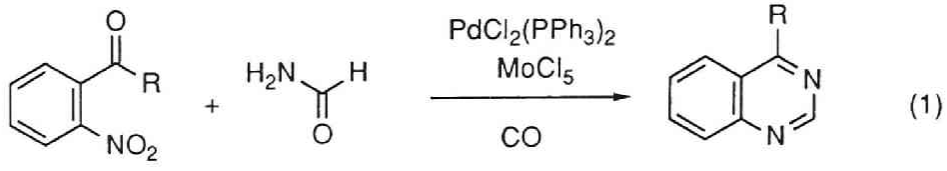
Synthesis of *N*-heterocyclic compounds using transition-metal catalysts is one of the most stimulating fields and many approaches have already been reported.[1] In the course of our studies on transition-metal complex-catalyzed *N*-heterocyclization reactions,[2] we have recently developed palladium complex-catalyzed reductive *N*-heterocyclization of nitroarenes. For example, palladium complex-tin(II) chloride system effectively catalyzed the synthesis of 2*H*-indazoles from *N*-(2-nitrobenzylidene)amines,[3a] and indoles from *o*-nitrostyrenes.[3b] More recently, we have also reported ruthenium- or platinum complex-catalyzed novel synthesis of 4(3*H*)-quinazolinone derivatives from *N*-(2-nitrobenzoyl)amides.[3c]

Since Griess has succeeded in the first synthesis of 2-cyano-3,4-dihydro-4-oxoquinazoline by the reaction of cyanogen with anthranilic acid in 1869,[4] a large number of quinazoline derivatives has been synthesized. In spite of their biological and industrial interests, however, catalytic synthesis of them are rarely reported. In this chapter, we report the first example of the catalytic synthesis of quinazoline derivatives from the intermolecular reductive *N*-heterocyclization of 2-nitrobenzaldehydes or 2-nitrophenyl ketones with formamide catalyzed by palladium complex molybdenum(V) chloride system

[Results and Discussion]

In the presence of a catalytic amount of $PdCl_2(PPh_3)_2$ and $MoCl_5$ under 20 $kgcm^{-2}$ of initial carbon monoxide pressure, the reductive *N*-heterocyclization of 2-nitrobenzaldehydes or 2-nitrophenyl ketones with

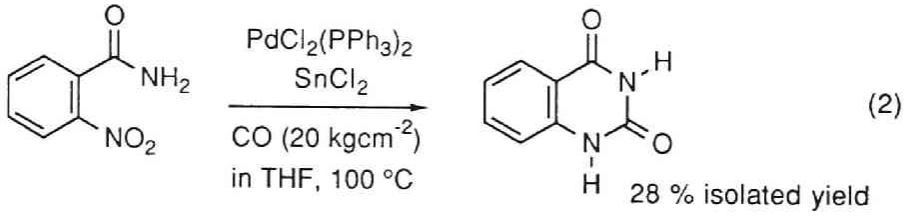
formamide effectively proceeded to give the corresponding quinazoline derivatives in moderate yields (eq 1). The representative results are summarized in Table I.



(1)

The reaction of 2-nitrobenzaldehyde, 2'-nitroacetophenone, 5'-methyl-2'-nitroacetophenone, and 2'-nitropropiophenone with formamide afforded the corresponding quinazoline derivatives in 19-46% yields (Runs 1-4). In the presence of molybdenum(V) chloride, 7-chloroquinazoline was obtained from 4'-chloro-2'-nitrobenzaldehyde in only 8% yield, but by the use of tin(II) chloride the yield of 7-chloroquinazoline increased to 18% (Run 5). Furthermore, from the reaction of methyl 2-nitrobenzoate, 4-hydroxyquinazoline was obtained in 40% yield (Run 6). When acetamide was employed instead of formamide, only a trace amount of the corresponding 2-substituted quinazoline was obtained.

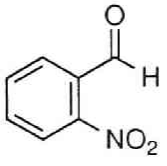
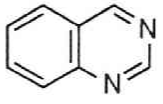
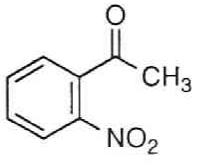
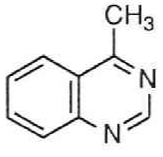
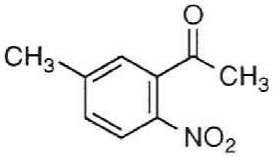
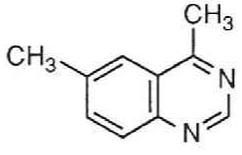
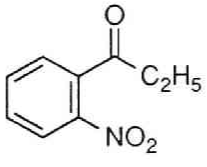
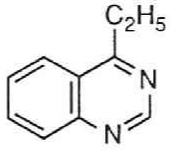
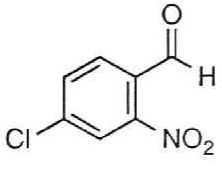
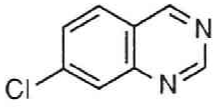
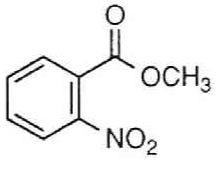
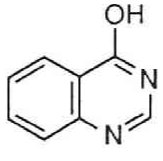
In the case of 2-nitrobenzamide, reductive *N*-carbonylation reaction proceeded alternatively to give 1,3-dihydro-2,4-quinazolidinone in 28% yield (eq 2).



(2)

Catalytic activities of several transition-metal complexes were examined in the reaction of 2-nitrobenzaldehyde with formamide and results are summarized in Table II.

Table I. Synthesis of Quinazoline Derivatives via Palladium-Catalyzed Intermolecular Reductive *N*-Heterocyclization of 2-Nitrobenzaldehydes and 2-Nitrophenyl Ketones with Formamide[a]

Run	Substrate	Product	Yield/%[b]
1			(46)
2			44
3			44
4			19
5[c]			18
6			40

a) Substrate (2.0 mmol), $PdCl_2(PPh_3)_2$ (0.10 mmol), $MoCl_5$ (1.0 mmol), formamide (5.0 ml) under CO (20 $kgcm^{-2}$) at 120 °C for 16 h. b) Isolated yields (GLC yield). c) Instead of $MoCl_5$, $SnCl_2$ (1.0 mmol) was employed.

Table II. Catalytic Activities of Several Transition-Metal Complexes in the Synthesis of Quinazoline from the Intermolecular Reductive *N*-Heterocyclization of 2-Nitrobenzaldehyde with formamide[a]

Run	Catalyst	Additive	Yield/%[b]
7	$PdCl_2(PPh_3)_2$	$SnCl_2$	36
8	$PdCl_2(PPh_3)_2$	-	12
9	$PdCl_2(PBu_3)_2$	$SnCl_2$	30
10[c]	$PdCl_2$(bipy)	$SnCl_2$	28
11	$PdCl_2(PhCN)_2$	$SnCl_2$	33
12	$RhCl(PPh_3)_3$	$SnCl_2$	17
13	$PtCl_2(PPh_3)_2$	$SnCl_2$	12
14	$NiCl_2(PPh_3)_2$	$SnCl_2$	5
15	$RuCl_2(PPh_3)_3$	$SnCl_2$	4

a) 2-Nitrobenzaldehyde (3.0 mmol), formamide (5.0 ml), catalyst (0.10 mmol), additive (1.0 mmol) under CO (20 $kgcm^{-2}$) at 100 °C for 16 h. b) Determined by GLC. c) bipy = 2,2'-bipyridine.

Table III. Effect of Lewis Acids[a]

Run	Additive	Yield/%[b]
1[c]	$MoCl_5$	46
16	$MoCl_5$	43
7	$SnCl_2$	36
17	$FeCl_3$	36
18	$AlCl_3$	19
19	$ZnCl_2$	15

a) 2-Nitrobenzaldehyde (3.0 mmol), $PdCl_2(PPh_3)_2$ (0.10 mmol), additive (1.0 mmol), formamide (5.0 ml) under CO (20 $kgcm^{-2}$) at 100 °C for 16 h. b) Determined by GLC. c) At 120 °C.

As in our previously reported results,[3] the addition of co-catalyst such as tin (II) chloride improved the catalytic activity. As shown in Table II, palladium complex combined with tin (II) chloride showed a good catalytic activity (Runs 7 and 8) and phosphorous ligands did not affect the present reaction (Runs 7 and 9-11). Catalytic activities of other group VIII metal complexes were quite low (Runs 12 - 15).

Effect of several Lewis acids employed as a co-catalyst is shown in Table III. $MoCl_5$ was the most effective co-catalyst (Run 1). $SnCl_2$ and $FeCl_3$ also showed moderate activity (Runs 7, 16, and 17), but $AlCl_3$ and $ZnCl_2$ were ineffective (Runs 18 and 19). We now consider that the molybdenum (V) chloride could work as an effective co-catalyst or ligand of the active catalyst, since Braunstein and Kervennal et al. have already reported that a catalyst derived from a mixed metal cluster, $Pd_2Mo_2(\eta^5\text{-}C_5H_5)_2(CO)_6(PPh_3)_2$, showed high catalytic activity for the reductive *N*-carbonylation of nitrobenzene to phenyl isocyanate.[5]

Furthermore, an effect of the reaction temperature was shown in Figure 1. The optimized temperature was 120 °C and the best yield of quinazoline was 46%.

In the absence of palladium complex and/or co-catalyst, 2-nitrobezaldehyde reacted with formamide to give the corresponding 2-nitrobenzaldiformamide (eq 3). Indeed, Ittyerah et al. have already reported that 2-nitrobenzaldehyde reacted with formamide at 60-70°C for 8 hours to afford the corresponding 2-nitrobenzaldiformamide in 40% yield.[6] Moreover, Adachi et al. have already reported that quinazolines were prepared by an intramolecular cyclization of 2-nitrobenzaldiformamide using zinc/acetic acid or iron/hydrochloric acid as reducing agent.[7]

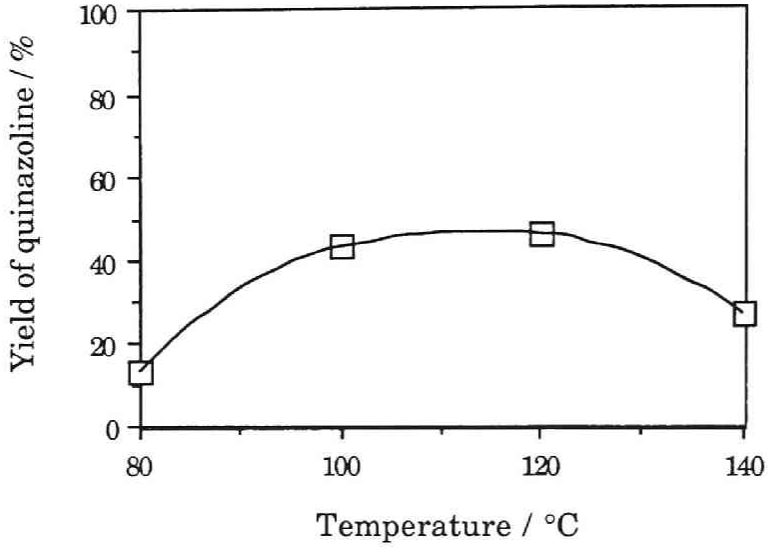
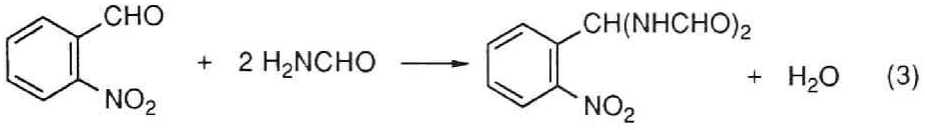


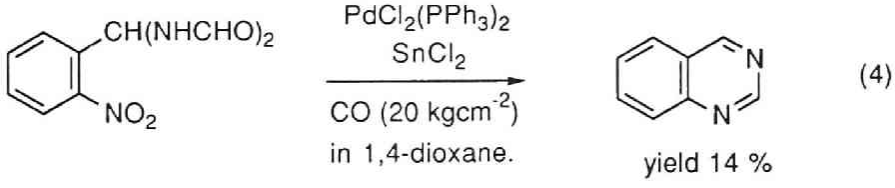
Figure 1. Effect of reaction temperature on palladium-catalyzed intermolecular reductive *N*-heterocyclization of 2-nitrobenzaldehye with formamide.

Reaction conditions: 2-nitrobenzaldehyde (3.0 mmol), $PdCl_2(PPh_3)_2$ (0.10 mmol), $MoCl_5$ (1.0 mmol), formamide (5.0 ml) under CO (20 $kgcm^{-2}$) for 16 h.



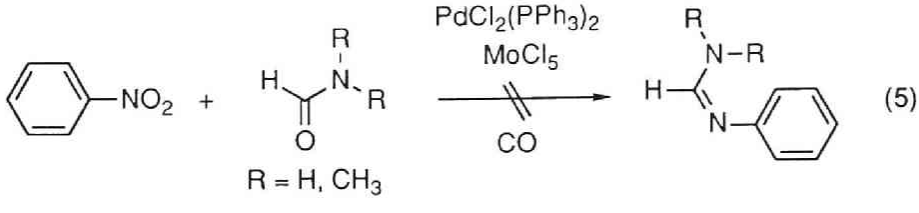
(3)

In our reaction, when the generated 2-nitrobenzaldiformamide was treated in the presence of a catalytic amount of $PdCl_2(PPh_3)_2$ and tin (II) chloride under CO pressure (20 $kgcm^{-2}$) at 100 °C for 16 h, quinazoline was actually obtained in 14 % yield (eq 4). This result suggests that the 2-nitrobenzaldiformamide seems to be one of the possible intermediates in the present reductive *N*-heterocyclization reaction.



(4)

On the other hand, we examined a possibility of the *intermolecular* reductive coupling of nitrobenzene with formamide or *N*,*N*-dimethylformamide. We have already succeeded in the synthesis of *N*-benzylideneaniline by the intermolecular reductive coupling of nitrobenzene with benzaldehyde using $PdCl_2(PPh_3)_2$ - $SnCl_2$ catalyst system.[3b] Under the present reaction conditions, however, the corresponding amidine was not obtained at all (eq 5).

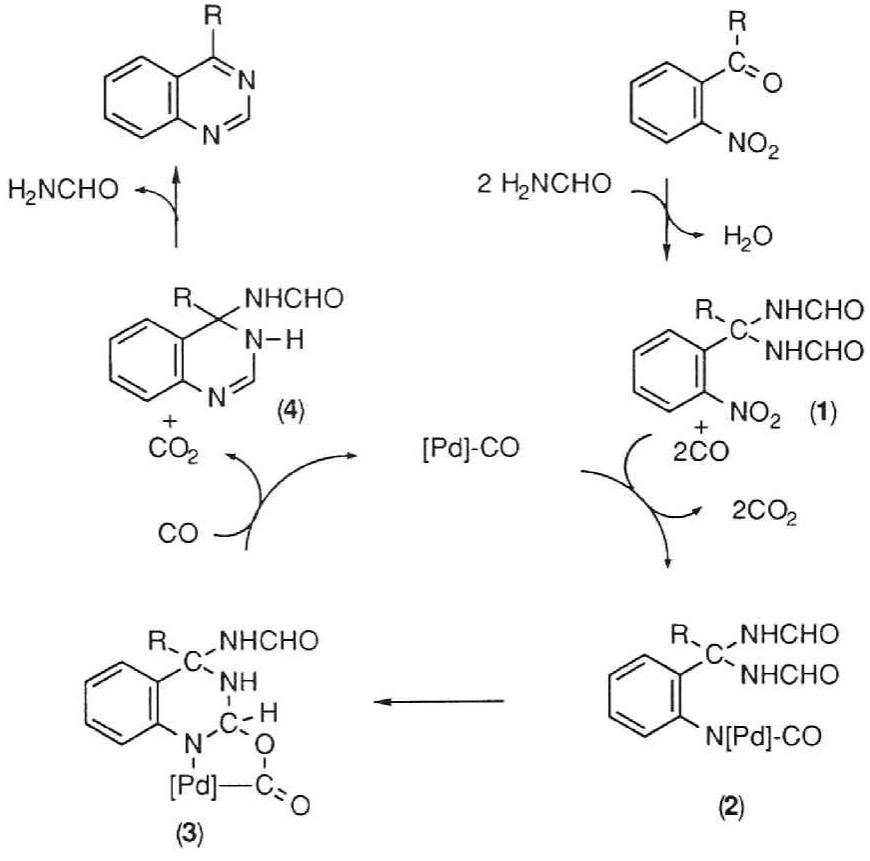


(5)

On the basis of the results mentioned above, a possible mechanism is illustrated in Scheme 1. At first, the carbonyl group of 2-nitrobenzaldehydes or 2-nitrophenyl ketones is condensed with two molecules of formamide to give

the corresponding bisamide (**1**). Secondly, deoxygenation of the nitro group of (**1**) with carbon monoxide and subsequent nucleophilic addition of the generated nitrene to carbonyl group of the bisamide affords the intermediate (**3**).[8] Then, the reductive elimination of 3,4-dihydro-4-(*N*-formylamino)-quinazoline (**4**) regenerates the active catalyst species together with the generation of CO_2. Finally, dehydroamidation of (**4**) gives the quinazoline derivative.[9]

Further studies on the mechanism and application of the reaction to organic synthesis are in progress.


R
N
N
H2NCHO
2 H2NCHO
H2O
NO2
C
O
NHCHO
N–H
(4)
(1)
CO2
CO
[Pd]-CO
2CO
2CO2
NHCHO
NH
H
O
[Pd]—C
O
N[Pd]-CO
(3)
(2)

Scheme 1

[Experimental Section]

Materials.

The reagents employed in this study were dried and purified before use by the usual procedures. Carbon monoxide (> 99.9 %) was used without further purification. Transition-metal complexes, such as $PdCl_2(PPh_3)_2$,[10] $PdCl_2(PBu_3)_2$,[11] $PdCl_2$(bipy),[12] $PdCl_2(PhCN)_2$,[13] $RhCl(PPh_3)_3$,[14] $PtCl_2(PPh_3)_2$,[15] $NiCl_2(PPh_3)_2$,[16] and $RuCl_2(PPh_3)_3$[17] were prepared by the literature's methods. $MoCl_5$, $SnCl_2$, $FeCl_3$, $AlCl_3$, and $ZnCl_2$ were commercially available and used without further purification. 2'-Nitropropiophenone and 5'-methyl-2'-nitroacetophenone were prepared by the literature's method.[18]

General Procedures.

A mixture of 2-nitrobenzaldehyde (2.0 mmol), $PdCl_2(PPh_3)_2$ (0.10 mmol), $MoCl_5$ (1.0 mmol), and dry formamide (5.0 ml) was placed in a 50 ml stainless steel autoclave (Yuasa Giken; SUS 316) equipped with a glass liner and a magnetic stirring bar. The unit was sealed and then purged three times with 20 $kgcm^{-2}$ pressurization-depressurization cycles of carbon monoxide. The reactor was then pressurized to 20 $kgcm^{-2}$ (at room temperature) with carbon monoxide, and heated to 120 °C within 10 min with stirring, and held at this temperature for 16 h. The reaction was terminated by rapid cooling, and gaseous products were discharged. The resulting brown solution was analyzed by GLC and FT-IR. Then, water (150 ml) was added to the reaction mixture and organic products were extracted by ether (50 ml × 3). The ether solution was dried by anhydrous Na_2SO_4 and after evaporation of ether, the products were isolated by Kugelrohr distillation. The identification of the products was confirmed by FT-IR, ^1H- and ^{13}C-NMR, elemental analyses and GC-MS. The GLC analyses were carried out on Shimadzu GC-8A

chromatographs equipped with glass columns (3 mm i. d. × 3m) packed with Silicone OV-17 (2 % on Chromosorb W(AW-DMCS), 80-100 mesh), PEG-HT (5 % on Uniport HP, 60-80 mesh). The IR spectra were measured on a Shimadzu FTIR-8100. The ^{1}H-NMR spectra were recorded at 270 MHz with a JEOL GSX-270 spectrometer. ^{13}C-MNR spectra were recorded at 25.05 MHz with JEOL JNM FX-100 spectrometer and/or 67.8 MHz with JEOL GSX-270 spectrometer. Samples were dissolved in $CDCl_3$, and the chemical shift values were expressed in relative to Me_4Si as an internal standard. Mass spectra (MS) were obtained on a Shimadzu QP-2000 spectrometer. The spectral and analytical data of the products are shown below.

Quinazoline: colorless solid; bp 150 °C / 10 mmHg(Kugelrohr distillation); ^{1}H-NMR($CDCl_3$, 270 MHz) δ 7.64(ddd, 1H, H-6, J=8.1, 6.8, 1.2Hz), 7.87-7.93(m, 2H, H-7,8), 8.03(d, 1H, H-8, J=8.8Hz), 9.33(s, 1H, H-2), 9.39(s, 1H, H-4); ^{13}C-NMR($CDCl_3$, 25.00MHz) δ 126.4(s, C_{4a}), 126.9(d, C_5), 127.7(d, C_6), 128.0(d, C_8), 133.9(d, C_7), 149.6(s, C_{8a}), 154.8(d, C_2); mass spectrum (electron impact) m/e. 130(M^+ , base-peak), 103(M^+-CHN, 71.5), 76(M^+-2CHN, 56.3).

4-Methylquinazoline: colorless solid; bp 170 °C / 10 mmHg(Kugelrohr distillation); ^{1}H-NMR($CDCl_3$, 270 MHz) δ 2.94(s, 3H, -CH_3), 7.62(ddd, 1H. H-6, J=8.3, 6.8, 1.2 Hz), 7.87(ddd, 1H, H-7, J=8.3, 6.8, 1.5 Hz), 8.01(d, 1H, H-5, J=8.3 Hz), 8.07(ddd, 1H, H-8, J=8.3, 1.2, 0.7Hz), 9.16(s, 1H, H-2); ^{13}C-NMR($CDCl_3$, 67.8 MHz) δ 21.69(-CH_3), 124.43(C_{4a}), 125.03(C_5), 127.64(C_6), 128.86(C_8), 133.72(C_7), 149.47(C_{8a}), 154.39(C_2), 168.27(C_4); mass spectrum (electron impact) m/e. 144(M^+, base-peak), 129(M^+-CH_3, 25.3), 103(M^+-CH_3CN, 32.8), 76(M^+-CH_3CNCHN, 30.4).

4,6-Dimethylquinazoline: colorless solid; bp 250 °C / 10 mmHg(Kugelrohr distillation); ^{1}H-NMR($CDCl_3$, 270 MHz) δ 2.55(s, 3H, -C*H*$_3$), 2.89(s, 3H, -C*H*$_3$), 7.67(dd, 1H, H-7, J=8.5, 2.0Hz), 7.78(m, 1H. H-5), 7.89(d, 1H, H-8, J=8.5Hz), 9.10(s, 1H, H-2); ^{13}C-NMR($CDCl_3$, 25.05 MHz) δ 21.6(q, -*C*H$_3$), 21.8(q, -*C*H$_3$), 123.5(d, C_5), 124.0(s, C_{4a}), 128.3(d, C_8), 135.4(d, C_7), 137.3(s, C_6), 147.7(s, C_{8a}), 153.4(d, C_2), 166.9(s, C_4); mass spectrum (electron impact) m/e. 158(M^+, base-peak), 143(M^+-CH_3, 18.4), 117(M^+-CH_3CN, 18.1), 90(M^+-CH_3CNCHN, 31.0).

4-Ethylquinazoline: colorless liquid; bp 200 °C / 5 mmHg(Kugelrohr distillation); ^{1}H-NMR($CDCl_3$, 270 MHz) δ 1.47(t, 3H, -C*H*$_3$, J=7.6Hz), 3.32(q, 2H, -C*H*$_2$-, J=7.6Hz), 7.64(t, 1H, H-6), 7.88(t, 1H, H-7), 8.04(d, 1H, H-5, J=8.2Hz), 8.13(d, 1H, H-8, J=8.3Hz), 9.23(s, 1H, H-2); ^{13}C-NMR($CDCl_3$, 67.8 MHz) δ 12.71(-*C*H$_3$), 27.71(-*C*H$_2$-), 123.75(C_{4a}), 124.56(C_5), 127.54(C_6), 129.14(C_8), 133.52(C_7), 149.75(C_{8a}), 154.64(C_2), 172.49(C_4); mass spectrum (electron impact) m/e. 158(M^+, 67.9), 157(M^+-H, base-peak), 130(35.8), 103(M^+-EtCN, 29.7), 76(M^+-EtCNCHN, 36.4).

7-Chlorquinazoline: colorless solid; bp 200 °C / 10 mmHg(Kugelrohr distillation); ^{1}H-NMR($CDCl_3$, 270 MHz) δ 7.64(dd, 1H, H-6, J=8.8, 2.0Hz), 7.90(d, 1H, H-5, J=8.8Hz), 8.07(d, 1H, H-8, J=2.0Hz), 9.35(s, 1H, H-2), 9.40(s, 1H, H-4); mass spectrum (electron impact) m/e. 166(M[^{37}Cl]$^+$, 33.8), 164(M[^{35}Cl]$^+$, base-peak), 137(M[^{35}Cl]$^+$-CHN, 48.6), 110(M[^{35}Cl]$^+$-2CHN, 34.1).

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Part II Ruthenium Complex-Catalyzed Deoxygenative Transformation of Oximes Using Carbon Monoxide

Chapter 5

Ruthenium Complex-Catalyzed Selective Deoxygenation of Ketoximes to Ketimines

[Summary]

$Ru_3(CO)_{12}$ shows a high catalytic activity for the selective deoxygenation of various ketoximes to the corresponding ketimines under carbon monoxide pressure (20 $kgcm^{-2}$). For the deoxygenation of propiophenone oxime, ethyl phenyl ketimine was obtained in 100% yield. In case of easily enolizible acetoxime, the deoxygenation and subsequent trimerization of the generated imine via elimination of ammonia proceeds to give 2,2,4,4,6-pentamethyl-2,3,4,5-tetrahydropyrimidine in 38 % yield. On the other hand, aldoximes such as heptanal oxime were only dehydrated to the corresponding nitriles under the same reaction conditions.

[Introduction]

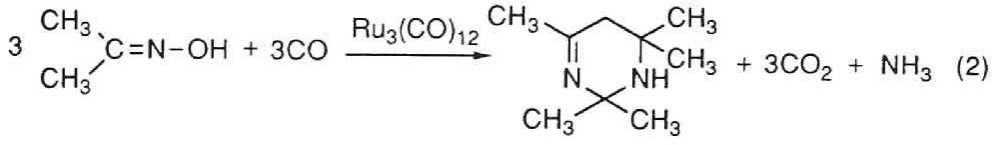
Since organic molecules including azomethine group (*i.e.*, $\rangle C{=}N-$) are important as both synthetic and biologic intermediates, various approaches for the construction of the azomethine group have been reported.[1] One of the elegant synthetic application of azomethine compounds is the synthesis of β-lactams by the photochemical reaction of chromium carbene complexes with imines reported by Hegedus et al.[2]

As for the synthesis of ketimines, which can often be used to regenerate the parent ketones,[3] examples are those including the reaction of ketones with ammonia using potassium hydroxide,[4] and the decomposition of nitrile Grignard complex by dry HCl, anhydrous ammonia[5] or absolute methanol.[6] More intriguing and simple method is deoxygenation of ketoximes using transition-metal complexes such as $TiCl_3$,[7] chromous (II) acetate,[8] peroxopalladium,[9] $Fe(CO)_5$,[10,11] and $Fe_2(CO)_9$.[11] However, a stoichiometric or excess amount of transition-metal complexes is always indispensable for all of these reactions and *true catalytic* deoxygenation of ketoximes to ketimines has not yet been reported.

In the course of our study on ruthenium complex-catalysis,[12] we found that $Ru_3(CO)_{12}$ showed a high catalytic activity for the selective deoxygenation of ketoximes to ketimines using carbon monoxide as a reducing agent (eq 1)

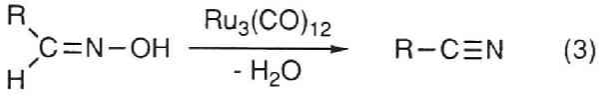
$$\begin{matrix} R^1 \\ \diagdown \\ \quad C{=}N{-}OH \\ \diagup \\ R^2 \end{matrix} + CO \xrightarrow{Ru_3(CO)_{12}} \begin{matrix} R^1 \\ \diagdown \\ \quad C{=}N{-}H \\ \diagup \\ R^2 \end{matrix} + CO_2 \qquad (1)$$

Among the oximes, acetoxime and cyclohexanone oxime firstly generated the corresponding ketimines but they easily isomerized to enamines to give the corresponding trimers by elimination of ammonia (eq 2).



(2)

In contrast to ketoximes, aldoximes were only dehydrated to give the corresponding nitriles (eq 3)



(3)

[Results and Discussion]

(I) $Ru_3(CO)_{12}$-Catalyzed Selective Deoxygenation of Ketoximes to Ketimines and Dehydration of Aldoximes to Nitriles

Catalytic activities of several ruthenium and other group VIII metal complexes were examined in the deoxygenation of propiophenone oxime and results are summarized in Table I.

In the presence of a catalytic amount of $Ru_3(CO)_{12}$, propiophenone oxime was smoothly deoxygenated to give the corresponding ethyl phenyl ketimine in 100% yield. After the deoxygenation of propiophenone oxime (Run 1), CO_2 was generated in 85% yield based on the amount of propiophenone oxime together with the corresponding ketimine. This result indicates that carbon monoxide effectively functioned as a deoxygenating reagent. Other transition-metal complexes such as $Ru(CO)_3(PPh_3)_2$, $Fe(CO)_5$,[10,11] $Fe_3(CO)_{12}$ showed some catalytic activity (Runs 2-4), but $RuCl_3 \cdot nH_2O$ and $RuCl_2(PPh_3)_3$ showed no catalytic activity under the same reaction conditions (Runs 5 and 6). When $Co_2(CO)_8$ and $Rh_6(CO)_{16}$[13] were employed in the present reaction,

the selectivity of the corresponding ketimines considerably decreased and unidentified high boiling products were obtained (Runs 7 and 8).

Table I. Catalytic Activities of Several Transition-Metal Complexes[a]

Run	Catalyst / mmol		Conv.[b] / %	Yield[b] / %	Selectivity[c] / %
1	$Ru_3(CO)_{12}$	(0.10)	100	100	100
2	$Ru(CO)_3(PPh_3)_2$	(0.30)	41	32	78
3	$Fe(CO)_5$	(0.46)	16	4	25
4	$Fe_3(CO)_{12}$	(0.10)	30	4	13
5	$RuCl_3 \cdot nH_2O$	(0.30)	32	0	0
6	$RuCl_2(PPh_3)_3$	(0.30)	5	trace	-
7	$Co_2(CO)_8$	(0.15)	81	31	38
8	$Rh_6(CO)_{16}$	(0.05)	100	36	36

a) Propiophenone oxime (5.0 mmol), benzene (5.0 ml) under CO (20 $kgcm^{-2}$) at 100 °C for 4 h. b) Determined by GLC. c) Selectivity = (Yield of ketimine / Conv. of ketoxime) × 100.

Effects of the reaction conditions, which were examined with propiophenone oxime (5.0 mmol) in the presence of $Ru_3(CO)_{12}$ catalyst, are shown in Table II and Figure 1.

When the amount of $Ru_3(CO)_{12}$ was reduced to 0.05 mmol (a half amount of Run 1), the conversion of propiophenone oxime decreased to 62% (Run 9), and at 80 °C, the catalytic activity was rather low (Run 10). Concerned with the carbon monoxide pressure (Figure 1), below 10 $kgcm^{-2}$, the yield of the corresponding ketimine decreased drastically and carbon monoxide pressure of over 20 $kgcm^{-2}$ is necessary for the present reaction.

Table II. Effect of Reaction Conditions[a]

Run	$Ru_3(CO)_{12}$ / mmol	Temp. / °C	Conv.[b] / %	Yield[b] / %	Selectivity[c] / %
1	0.10	100	100	100	100
9	0.05	100	62	58	92
10	0.10	80	73	57	78

a) Propiophenone oxime (5.0 mmol), benzene (5.0 ml) under CO (20 $kgcm^{-2}$) for 4 h. b) Determined by GLC. c) Selectivity = (Yield of ketimine / Conv. of ketoxime) × 100.

Various ketoximes including aromatic, aliphatic and cyclic ketoximes were smoothly deoxygenated under the present reaction conditions to give the corresponding ketimines in 77 100% yields. Results are summarized in Table III. Isopropyl phenyl ketimine was obtained in 91 % isolated yield from isopropyl phenyl ketoxime (Run 12). Although ketimines containing halogen atom and cyclic ketimines were hard to be prepared by previously reported methods,[4,5,6] methyl 4-chlorophenyl ketimine and 2,6-dimethylcyclohexanone imine were easily obtained in high isolated yields by the present catalyst system (Runs 14 and 15).

On the other hand, deoxygenation of aldoximes to the corresponding aldimines did not proceed under the present reaction conditions. Heptanal oxime and benzaldoxime were only dehydrated at 100 150 °C to give heptanenitrile and benzonitrile in 32% and 22% yield, respectively (Runs 17 and 18). Similar rhodium-catalyzed dehydration of aldoximes to the corresponding nitriles has already been reported by Kaneda et al.[13]

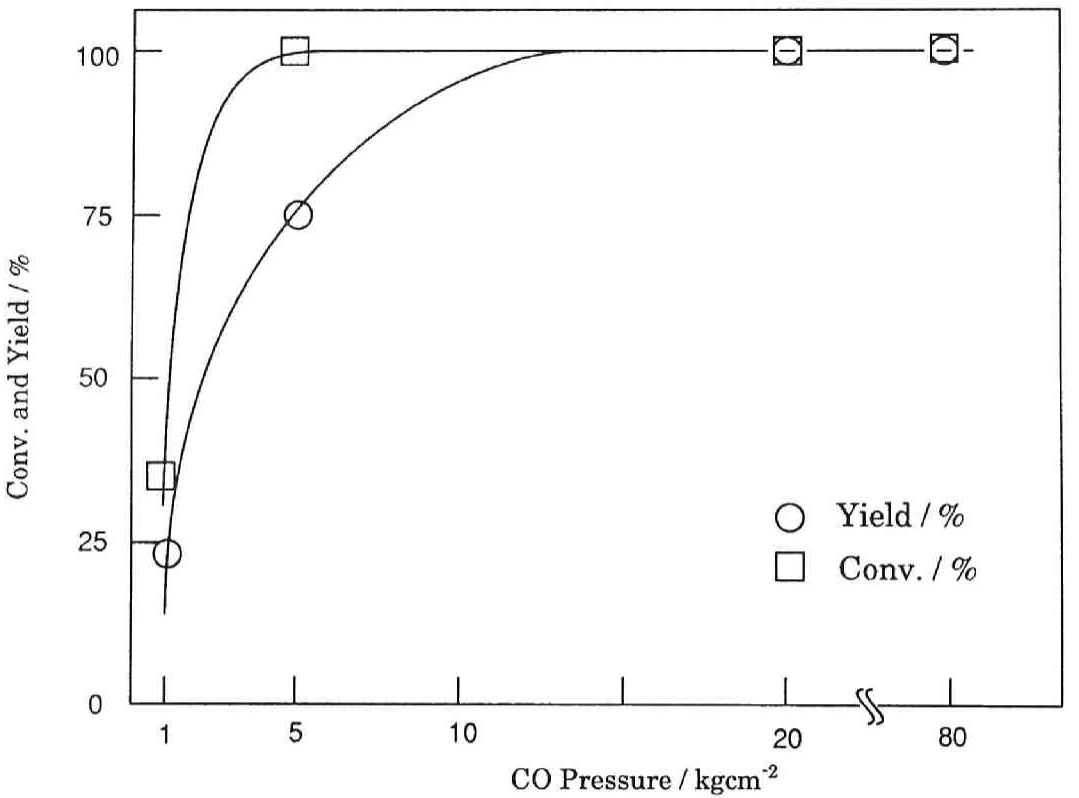
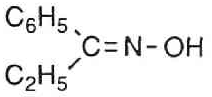
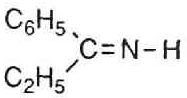
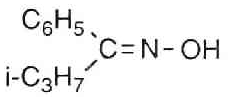
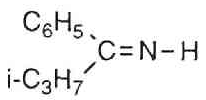
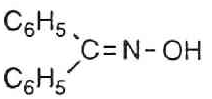
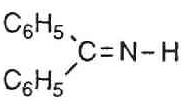
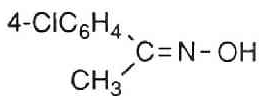
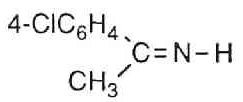
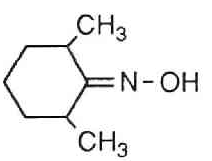
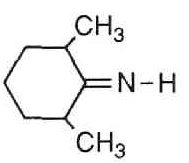
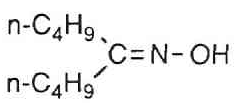
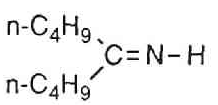


Figure 1. Effect of carbon monoxide pressure on the ruthenium complex-catalyzed deoxygenation of propiophenone oxime.
Reaction conditions: propiophenone oxime (5.0 mmol), $Ru_3(CO)_{12}$ (0.10 mmol), benzene (5.0 ml) at 100 °C for 4h.

Table III. $Ru_3(CO)_{12}$-Catalyzed Selective Deoxygenation of Various Ketoximes[a]

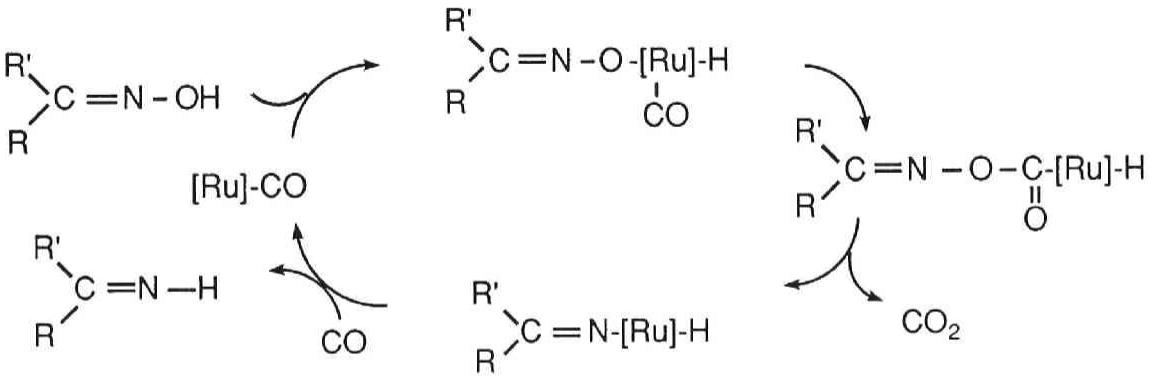
Run	Oxime	Product	Yield/%[b]
11			(100)
12			91
13			82
14			77
15			75
16[c]			82
17[d]	$n\text{-}C_6H_{13}CH{=}N\text{-}OH$	$n\text{-}C_6H_{13}C{\equiv}N$	32
18[d,e]	$C_6H_5CH{=}N\text{-}OH$	$C_6H_5C{\equiv}N$	22

a) Oxime (5.0 mmol), $Ru_3(CO)_{12}$ (0.10 mmol), benzene (5.0 ml) under CO (20 $kgcm^{-2}$) at 100°C for 4h. b) Isolated yields (GLC yield). c) For 8h. d) The corresponding aldimine was not detected at all. e) At 150 °C

The most plausible mechanism of the present deoxygenation reaction is illustrated in Scheme 1. Under the present reaction conditions, *O*-benzyl propiophenone oxime and *O*-acetyl acetophenone oxime having no O-H bond, were not converted at all. This result suggests that the initial step of the present reaction would be an oxidative addition of ketoxime to an active catalyst center to afford the hydrido(oximato)ruthenium intermediate. After carbonyl insertion and following decarboxylation, the ketimine was obtained via a reductive elimination of hydrido(alkylideneamido)ruthenium intermediate. In fact, Wilkinson et al. reported the formation of $Ru(oximato)_2(PPh_3)_2$ by the O-H bond cleavage of ketoximes using $RuCl_2(PPh_3)_3$ and NaOH (Figure 2).[14]

(II) $Ru_3(CO)_{12}$-Catalyzed Synthesis of 2,3,4,5-Tetrahydropyrimidine Derivatives by Deoxygenation of Acetoxime, Cyclohexanone Oxime, and Cyclopentanone Oxime

As can be readily seen from Table IV, deoxygenation of acetoxime, cyclohexanone oxime, and cyclopentanone oxime give the corresponding 2,3,4,5-tetrahydropyrimidine derivatives under the present reaction conditions. They seem to be generated by the trimerizaion of the firstly generated ketimines, which were easily isomerized to the corresponding enamines. Enamines from the generated imines can react with another molecule of ketimine to give the corresponding 2-azadienes by the elimination of ammonia, and subsequently, [4 + 2] cycloaddition of this 2-azadiene with ketimine occurs to give the trimerized product (Scheme 2). A similar [4 + 2] cycloaddition of 2-azadienes with aldehydes has already been reported.[15]



Scheme 1

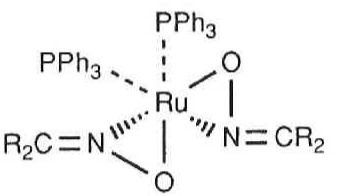
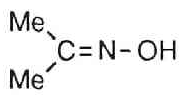
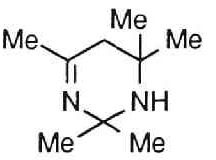
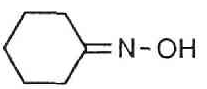
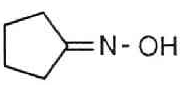
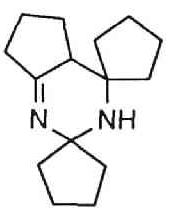
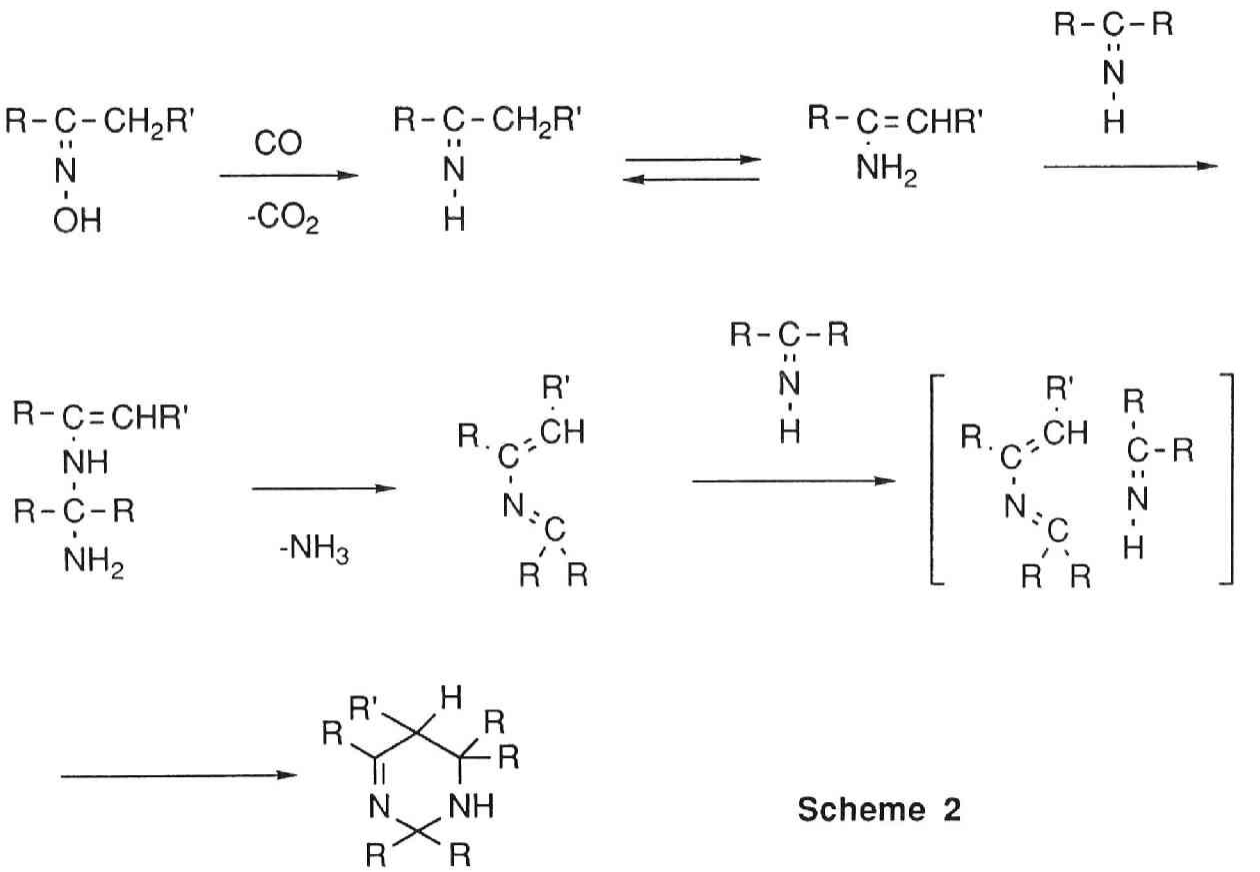


Figure 2. Bis(oximato)ruthenium complex

Table IV. Synthesis of 2,3,4,5-Tetrahydropyrimidine Derivatives[a]

Run	Ketoxime	Product	Yield/%[b]
19			38
20			68
21			64

a) Ketoxime (5.0 mmol), $Ru_3(CO)_{12}$ (0.10 mmol), benzene (5.0 ml) under CO (20 $kgcm^{-2}$) at 100 °C for 4 h. b) Isolated yield.



Scheme 2

(III) Stereochemistry of the Generated Ketimines

Although we can not control the stereochemistry of the generated ketimines, it has been reported that *syn* - *anti* isomerization of ketimines could be observed in some cases.[16] The ^{13}C-NMR and ^{1}H-NMR spectra of the generated ketimines exhibited a large temperature-dependence. For example, the stereochemistry of dibutyl ketimine was investigated at low (-85°C) to high (100°C) temperature by ^{13}C-NMR spectroscopy and the results are shown in Figure 3. At 27 °C (room temperature), two methylene carbons, directly attached to an imine carbon, appeared as a single broad signal and it suggests that *syn* - *anti* isomerization of ketimine was extremely rapid. This signal was split according to lowering the temperature, and below -60 °C, each methylene carbon was detected independently and the conformation of *syn* and *anti* isomers would be fixed. These results imply that it is quite difficult to maintain and control the stereochemistry of both the starting ketoximes and the generated ketimines under the present reaction conditions (at 100 °C). Indeed, Lambert et al. estimated that the activation energy of *syn* - *anti* isomerization of dibutyl ketimine is less than 5-7 kcal/mol.[16]

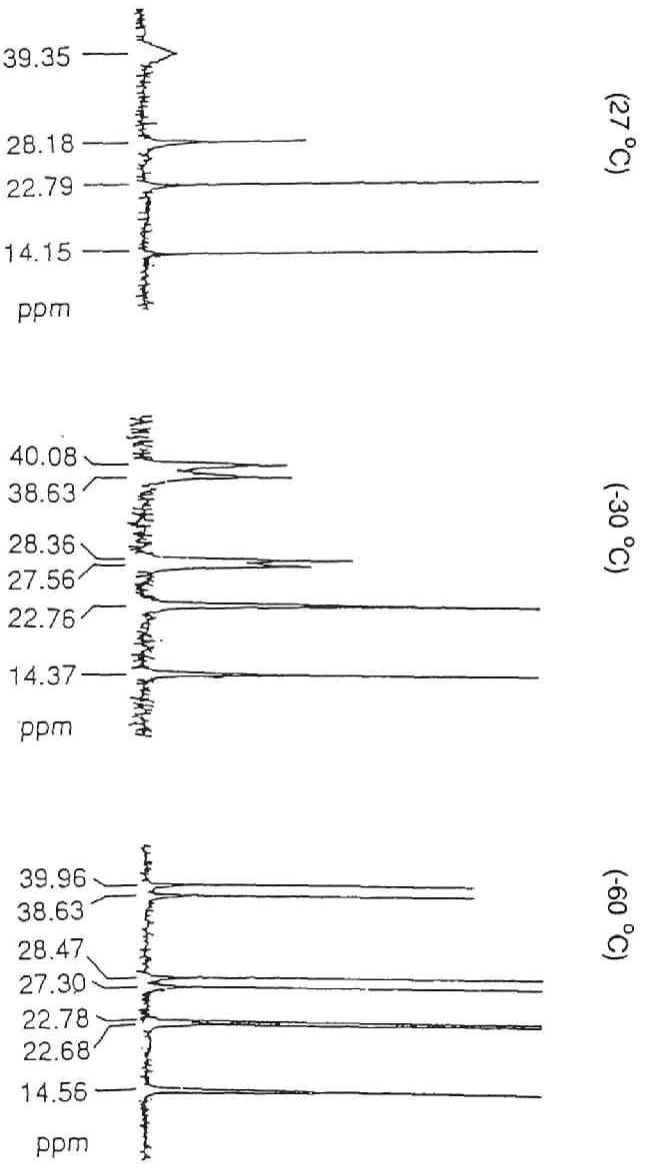


Figure 3. Temperature-dependence of ^{13}C-NMR spectra of dibutyl ketimine

[Experimental Section]

Materials.

The reagents employed in this study were dried and purified before use by the usual procedures. Carbon monoxide (> 99.9%) was used without further purification. $Ru(CO)_3(PPh_3)_2$,[17] $RuCl_2(PPh_3)_3$,[18] and $Rh_6(CO)_{16}$[19] were prepared by the literature's methods. $Ru_3(CO)_{12}$, $Fe_2(CO)_9$ and $Co_2(CO)_8$ were purchased from Strem Chemicals and only $Co_2(CO)_8$ was recrystallized from pentane before use. $Fe(CO)_5$ was purchased from Kanto Chemicals and used without further purification.

Preparation of Oximes.

Oximes were prepared by treatment of the corresponding carbonyl compounds (1 equiv.) with hydroxylamine hydrochloride (1.5 equiv.) and potassium hydroxide (1.5 equiv.) in methanol under reflux for several hours. Benzophenone oxime was prepared by the literature method.[20] The obtained crude products were purified by recrystallization from petroleum ether (boiling range 30 ~ 70 °C) or by distillation.

O-Acetylation of ketoximes were performed according to the literature's method.[21]

General Procedures.

A mixture of ketoxime (5.0 mmol), $Ru_3(CO)_{12}$ (0.10 mmol) and benzene (5.0 ml) was placed in a 50 ml stainless steel autoclave (Yuasa Giken; SUS 316) equipped with a glass liner and a magnetic stirring bar. The unit was sealed and then purged three times with 20 $kgcm^{-2}$ pressurization - depressurization cycles of carbon monoxide. The reactor was then pressurized to 20 $kgcm^{-2}$ with carbon monoxide (at room temperature), and heated to 100 °C within 15

min with stirring and held at this temperature for 4 h. The reaction was terminated by rapid cooling, and gaseous products were discharged. The resulting orange solution was analyzed by GLC.

Analytical Procedures.

All products were isolated by Kugelrohr distillation. The identification of the products was confirmed by ^{1}H-NMR, ^{13}C-NMR, IR, and GC-MS.

The GLC analyses were carried out on a Shimadzu GC-8A chromatograph equipped with columns (3 m i.d. x 3 m) packed with Silicone OV-17 (2 % on Chromosorb W(AW), 80-100 mesh), PEG-HT (5 % on Uniport HP, 60 - 80 mesh).

The IR spectra were measured on a Nicolet 5MX Fourier transform infrared spectrophotometer.

The ^{1}H-NMR spectra were recorded on JEOL JNM FX-90 (90 MHz) or JEOL GSX-270 spectrometer (270 MHz). ^{13}C-NMR spectra were recorded at 22.50 MHz with JEOL JNM FX-90 spectrometer and at 25.05 MHz with JEOL JNM FX-100 spectrometer. Samples were dissolved in $CDCl_3$, and the chemical shift values were expressed in relative to Me_4Si as an internal standard.

Mass spectra (MS) were obtained on Shimadzu QP-1000 or QP-2000 spectrometers.

The analytical data of the products are described below.

Ethyl phenyl ketimine: colorless liquid; 130 °C / 25 mmHg(Kugelrohr distillation); IR(neat) 3238 cm^{-1} ($\nu_{N\text{-}H}$), 1620 cm^{-1} ($\nu_{C=N}$); ^{1}H-NMR($CDCl_3$)(90 MHz) δ 1.21(t, 3H, -C*H*$_3$), 2.99(q, 2H, -C*H*$_2$-), 6.97-8.08(m, 6H, phenyl, N*H*); ^{13}C-NMR($CDCl_3$)(25.00 MHz) δ 10.0(q, -*C*H$_3$), 29.9(t, -*C*H$_2$-), 126.0(d, phenyl), 128.1(d, phenyl), 129.8(d, phenyl), 138.6(s, phenyl), 178.9(s, *C*=N).

Methyl phenyl ketimine: colorless liquid; 190 °C / 15 mmHg(Kugelrohr distillation); IR(neat) 3229cm^{-1} (ν_{N-H}), 1624 cm^{-1} ($\nu_{C=N}$); ^{1}H-NMR($CDCl_3$)(90 MHz) δ 2.35(s, 3H, -C*H*$_3$), 7.12-8.07(m, 6H, phenyl, N*H*); ^{13}C-NMR($CDCl_3$)(25.00 MHz) δ 25.8(q, -*C*H$_3$), 126.3(d, phenyl), 128.3(d, phenyl), 130.3(d, phenyl), 138.6(s, phenyl), 175.0(s, *C*=N).

Isopropyl phenyl ketimine: colorless solid; 190 °C / 15 mmHg(Kugelrohr distillation); IR(neat) 3290 cm^{-1} (ν_{N-H}), 1617 cm^{-1} ($\nu_{C=N}$); ^{1}H-NMR($CDCl_3$)(90 MHz) δ 1.13(d, 6H, -CH(C*H*$_3$)$_2$), 3.11(septet, 1H, -C*H*(CH$_3$)$_2$), 7.29-7.75(m, 6H, phenyl, N*H*); ^{13}C-NMR($CDCl_3$)(22.50 MHz) δ 20.2(q, -CH(*C*H$_3$)$_2$), 33.6(d, *C*H(CH$_3$)$_2$), 126.4(d, phenyl), 128.4(d, phenyl), 129.8(d, phenyl), 139.5(s, phenyl), 183.8(s, *C*=N).

Diphenyl ketimine: colorless liquid; 200 °C / 1.0 mmHg(Kugelrohr distillation); IR(neat) 3252 cm^{-1} (ν_{N-H}), 1603 cm^{-1} ($\nu_{C=N}$); ^{1}H-NMR($CDCl_3$)(90 MHz) δ 7.19-7.70(m, phenyl, N*H*); ^{13}C-NMR($CDCl_3$)(22.50 MHz) δ 128.2(d, phenyl), 130.1(d, phenyl), 139.3(s, phenyl), 177.8(s, *C*=N).

Methyl 4-chlorophenyl ketimine: colorless liquid; 120 °C /0.6 mmHg(Kugelrohr distillation); IR(neat) 3233 cm^{-1} (ν_{N-H}), 1622 cm^{-1} ($\nu_{C=N}$); ^{1}H-NMR($CDCl_3$)(90 MHz) δ 2.36(s, 3H, -C*H*$_3$), 7.22-8.12(m, 5H, phenyl, N*H*); ^{13}C-NMR($CDCl_3$)(22.50 MHz) δ 26.3(q, -*C*H$_3$), 128.5(d, phenyl), 136.4(s, phenyl), 136.9(s, phenyl), 173.1(s, *C*=N).

2,6-Dimethylcyclohexanone imine: colorless liquid; 70 °C/10 mmHg(Kugelrohr distillation); IR(neat) 3387 cm^{-1} (ν_{N-H}), 1640 cm^{-1} ($\nu_{C=N}$); ^{1}H-NMR($CDCl_3$)(270 MHz) δ 1.05(d, 6H, -C*H*$_3$), 1.52-2.52(m, 8H, -C*H*$_2$-, -C*H*-), 7.33(s, 1H, N*H*); ^{13}C-

NMR($CDCl_3$)(25.00 MHz) δ 16(q, -CH_3), 26.0(t, 4-CH_2-), 37.3(t, 3,5-CH_2-), 41.6(d, CH-), 188.4(s, C=N).

Dibuthyl ketimine: colorless liquid; 120 °C / 4 mmHg(Kugelrohr distillation); IR(neat) 3367 cm^{-1} (ν_{N-H}), 1643 cm^{-1} ($\nu_{C=N}$); ^{1}H-NMR($CDCl_3$, 27 °C)(270 MHz) δ 0.93(t, -CH_3), 1.35(m, -CH_2CH_3), 1.55(m, -$CH_2CH_2CH_5$), 2.23(t, -$CH_2C_3H_7$), 8.96(s, NH), ; ^{13}C-NMR(toluene-d_8, 27 °C)(67.80 MHz) δ 14.15(q, -CH_3), 22.79(t, -CH_2CH_3), 28.18(t, -$CH_2C_2H_5$), 39.35(t, -$CH_2C_3H_7$), 181.49(s, C=N).

2,2,4,4,6-Pentamethyl-2,3,4,5-tetrahydropyrimidine: colorless liquid; 100 °C / 45 mmHg(Kugelrohr distillation); IR(neat) 3391 cm^{-1} (ν_{N-H}), 1668 cm^{-1} ($\nu_{C=N}$); ^{1}H-NMR($CDCl_3$)(270 MHz) δ 1.11(s, 6H, -CH_3), 1.37(s, 6H, -CH_3), 1.86(s, 2H, CH_2-), 1.95(s, 3H, -CH_3); ^{13}C-NMR($CDCl_3$)(25.00 MHz, NNE) δ 28.2(q, 1C, -CH_3), 30.5(q, 2C, -CH_3), 31.8(q, 2C, -CH_3), 41.2(t, 1C, -CH_2-), 47.1(s, 1C, -CN-), 70.1(s, 1C, -NCN-), 162.4(s, 1C, C=N), Ms, m/z 154(M^+).

5,6-Cyclohexa-dispiro[dicyclohexa-2,4]-2,3,4,5-tetrahydropyrimidine: colorless liquid; 200 °C / 5 mmHg(Kugelrohr distillation); IR(neat) 3295 cm^{-1} (ν_{N-H}), 1666 cm^{-1} ($\nu_{C=N}$); ^{13}C-NMR($CDCl_3$)(67.80 MHz) δ 21.57(t, -CH_2-), 21.96(t, -CH_2-), 22.52(t, -CH_2-), 22.59(t, -CH_2-), 26.05(t, -CH_2-), 26.38(t, -CH_2-), 26.44(t, -CH_2-), 29.20(t, -CH_2-), 29.46(t, -CH_2-), 35.61(t, -CH_2-), 38.30(t, -CH_2-), 38.46(t, -CH_2-), 40.82(t, -CH_2-), 42.50(t, -CH_2-), 46.49(d, -CH-), 50.11(s, -CN-), 70.13(s, -NCN-),169.61(s, C=N).

5,6-Cyclopenta-dispiro[dicyclopenta-2,4]-2,3,4,5-tetrahydropyrimidine: colorless liquid; 230 °C / 3 mmHg(Kugelrohr distillation); IR(neat) 3320 cm^{-1} (ν_{N-H}), 1660 cm^{-1} ($\nu_{C=N}$); ^{13}C-NMR($CDCl_3$)(25.00 MHz) δ 20.72(t, -CH_2-), 23.42(t, -CH_2-), 23.66(t, -CH_2-), 25.36(t, -CH_2-), 25.54(t, -CH_2-), 27.77(t, -CH_2-),

31.88(t, -CH_2-), 34.58(t, -CH_2-), 41.45(t, -CH_2-), 41.74(t, -CH_2-), 43.80(t, -CH_2-), 48.20(d, -CH-), 61.59(s, -CN-), 82.13(s, -NCN-), 173.08(s, C=N).

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Chapter 6

Ruthenium Complex-Catalyzed Selective Deoxygenation of Amidoximes to Amidines and its Application to the Facile Synthesis of Pyrimidines

[Summary]

$Ru_3(CO)_{12}$ shows a high catalytic activity for the selective deoxygenation of aromatic and heteroaromatic amidoximes to the corresponding amidines at 80 °C for 5 h under carbon monoxide pressure (5 $kgcm^{-2}$). For example, the deoxygenation of benzamidoxime afforded benzamidine in 82% yield. Furthermore, the present deoxygenation reaction of amidoximes catalyzed by $Ru_3(CO)_{12}$ was applied to the one-pot synthesis of pyrimidine derivatives. When the deoxygenation of amidoximes was carried out in the presence of 1,3-dicarbonyl compounds such as acetylacetone, acetylacetophenone, and ethyl acetoacetate, the corresponding pyrimidine derivatives, which were the condensation products of the generated amidines with 1,3-dicarbonyl compounds, were obtained in up to 93% yield.

[Introduction]

Organic molecules including amidino group are important as both synthetic and biological intermediates. Especially in the field of antibiotics, the amidine is one of the most important functional compounds and is found in the structures of amidinomycin[1], noformycin,[2] and netropsin[3]. So various approaches to the synthesis of amidines have already been reported.[4] Recently, Dondoni et al. have reported an intriguing and simple method for the deoxygenation of amidoximes to amidines. However, their reaction required a stoichiometric amount of iron pentacarbonyl ($Fe(CO)_5$) as a deoxygenating reagent.[5]

Among the various possible methods, we are interested in transition-metal complex-catalyzed selective deoxygenation of amidoximes to amidines. Since the amidoximes are readily available and stable crystalline compounds, their conversion to amidines by catalytic reaction seems preferable to the less satisfactory but more commonly employed methods.[6] In the course of our study on ruthenium complex catalysis,[7] we found that ruthenium complexes show a high catalytic activity for the selective deoxygenation of amidoximes to amidines, in which carbon monoxide was employed as an effective deoxygenating reagent.

Furthermore, the pyrimidine nucleus is also common to a large number of biologically active, naturally occurring compounds, and numerous approaches to its facile and widely applicable synthesis have been reported.[8] Among them, Pinner's pyrimidine synthesis, *i.e.*, the condensation reaction of amidines with 1,3-dicarbonyl compounds, is the most well-known and generally employed method.[9] So, when the present ruthenium-catalyzed deoxygenation of amidoximes to amidines was carried out in the presence of 1,3-dicarbonyl compounds such as acetylacetone, acetylacetophenone, and

ethyl acetoacetate, the subsequent condensation of the generated amidines with 1,3-dicarbonyl compounds proceeded smoothly to afford the corresponding pyrimidine derivatives.

In this chapter, we report full details of ruthenium-catalyzed selective deoxygenation of amidoximes to amidines and application of the present reaction to the facile and one-pot synthesis of pyrimidine derivatives.

[Results and Discussion]

Ruthenium Complex-Catalyzed Selective Deoxygenation of Amidoximes to Amidines

The deoxygenation of amidoximes smoothly proceeded in the presence of a catalytic amount of $Ru_3(CO)_{12}$ at 80 °C for 5 h under carbon monoxide pressure (5 $kgcm^{-2}$) to give the corresponding amidines in good yields (eq 1).

$$\mathrm{R{-}\underset{\underset{\mathrm{NOH}}{\|}}{C}{-}NH_2} + CO \xrightarrow{Ru_3(CO)_{12}} \mathrm{R{-}\underset{\underset{\mathrm{NH}}{\|}}{C}{-}NH_2} + CO_2 \qquad (1)$$

Firstly, various group VII and VIII metal complexes were used as catalyst precursors in the deoxygenation of benzamidoxime to benzamidine. The results are summarized in Table I.

Among the ruthenium complexes, $Ru_3(CO)_{12}$ showed the highest catalytic activity (Run 2) whereas $RuCl_3 \cdot nH_2O$ also showed some catalytic activity (Run 3). However, the catalytic activities of several ruthenium phosphine complexes (Runs 4 and 5) and $Ru(acac)_3$ (Run 6) were quite low. After the reaction of Run 2, the IR spectra of the resulting orange solution indicated only one strong absorption band at 2037 cm^{-1}, different from the absorption bands of $Ru_3(CO)_{12}$.[10] In addition, the reaction mixture of Run 3

($RuCl_3 \cdot nH_2O$) also showed the same absorption band at 2037 cm^{-1}.[11] So, the catalyst precursors which could be employed in the present reaction were those which are easily reduced to low-valent, probably zerovalent, amidoxime or amidine coordinated ruthenium carbonyl complexes under the present reaction conditions. Other transition metal carbonyl complexes such as $Rh_6(CO)_{16}$, $Co_2(CO)_8$ and $Fe(CO)_5$ showed some catalytic activities (Runs 8-10), but the catalytic activities of $Fe_3(CO)_{12}$, $Pd(PPh_3)_4$, and $Mn_2(CO)_{10}$ were quite low (Runs 11-13).

Table I. Catalytic Activities of Several Transition-Metal Complexes in the Deoxygenation of Benzamidoxime to Benzamidine[a]

Run	Catalyst /mmol		Conv./%[b]	Yield /%[b]	
				Amidine	Nitrile
1			12	1	2
2	$Ru_3(CO)_{12}$	(0.10)	100	52	34
3	$RuCl_3 \cdot nH_2O$	(0.30)	58	21	21
4	$RuCl_2(PPh_3)_3$	(0.30)	47	9	21
5	$Ru(CO)_3(PPh_3)_2$	(0.30)	29	4	23
6	$Ru(acac)_3$	(0.30)	24	1	14
7[c]	$Ru_3(CO)_{12}$	(0.10)	27	3	11
8	$Co_2(CO)_8$	(0.15)	54	13	12
9	$Fe(CO)_5$	(0.30)	41	11	24
10	$Fe_3(CO)_{12}$	(0.10)	47	4	41
11	$Pd(PPh_3)_4$	(0.30)	44	4	33
12	$Mn_2(CO)_{10}$	(0.15)	45	1	41
13	$Rh_6(CO)_{16}$	(0.05)	47	26	11

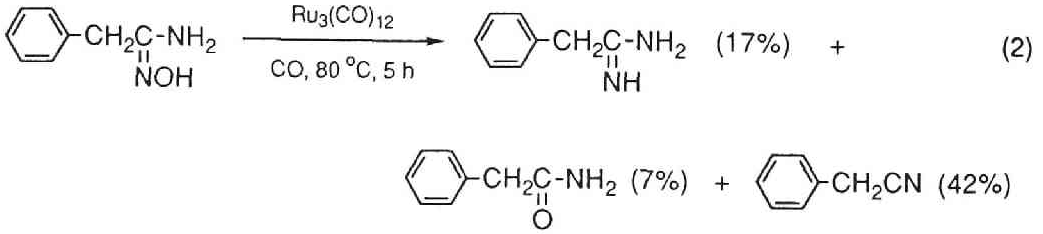
a) Benzamidoxime (5.0 mmol), THF (5.0 ml) under CO (20 $kgcm^{-2}$) at 100 °C for 4 h. b) Determined by GLC. c) Under H_2 (10 $kgcm^{-2}$) at 80 °C for 5 h.

After the deoxygenation of benzamidoxime (Run 1), carbon dioxide was generated in 49% yield based on the amount of benzamidoxime. Other reductants such as hydrogen (10 $kgcm^{-2}$) were not effective (Run 7). This

result clearly indicates that carbon monoxide actually functioned as an efficient deoxygenation reagent, and also stabilized an active catalyst species.

In any reactions in Table 1, a considerable amount of the corresponding nitriles was generated as a by-product (at 100 °C under CO (20 $kgcm^{-2}$)). So we tried to optimize the reaction conditions. Figures 1 and 2 show the effects of reaction temperature and CO pressure on the deoxygenation of benzamidoxime to benzamidine using $Ru_3(CO)_{12}$ catalyst. When CO pressure was kept at 20 $kgcm^{-2}$, the optimum reaction temperature was 80 °C. At lower temperatures, the conversion of benzamidoxime drastically decreased. Furthermore, at higher temperatures, the selectivity of benzamidine was reduced and at 120 °C, benzonitrile was formed as a major product (Fig. 1). At 80 °C, lower CO pressure resulted in the better yield of benzamidine, and the best result (82% yield of benzamidine) was obtained under 5 $kgcm^{-2}$ of initial carbon monoxide pressure (Fig. 2).

Various aromatic and heteroaromatic amidoximes could be employed in the present deoxygenation reaction (Table II). Benzamidoxime, 4-chlorobenzamidoxime, 4-methylbenzamidoxime, and 4-pyridinecarboxamidoxime were smoothly deoxygenated to the corresponding amidines in 45-82% yield. On the other hand, the deoxygenation of aliphatic amidoximes such as phenylacetamidoxime did not proceed selectively, and afforded phenylacetamidine in only 17% yield, together with phenylacetamide in 7% yield and benzyl cyanide in 42% yield (eq 2).



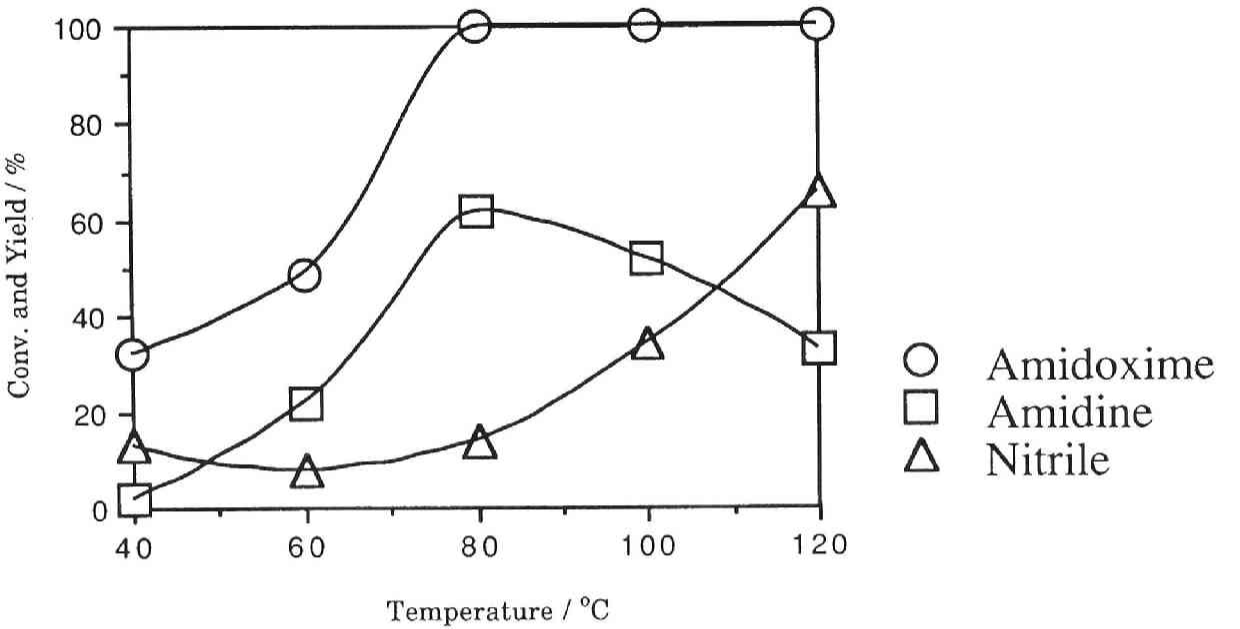


Figure 1. Effect of reaction temperature on $Ru_3(CO)_{12}$-catalyzed deoxygenation of benzamidoxime to benzamidine. Reaction conditions: benzamidoxime (5.0 mmol), $Ru_3(CO)_{12}$ (0.10 mmol), THF (5.0 ml) under CO 20 $kgcm^{-2}$ for 4h.

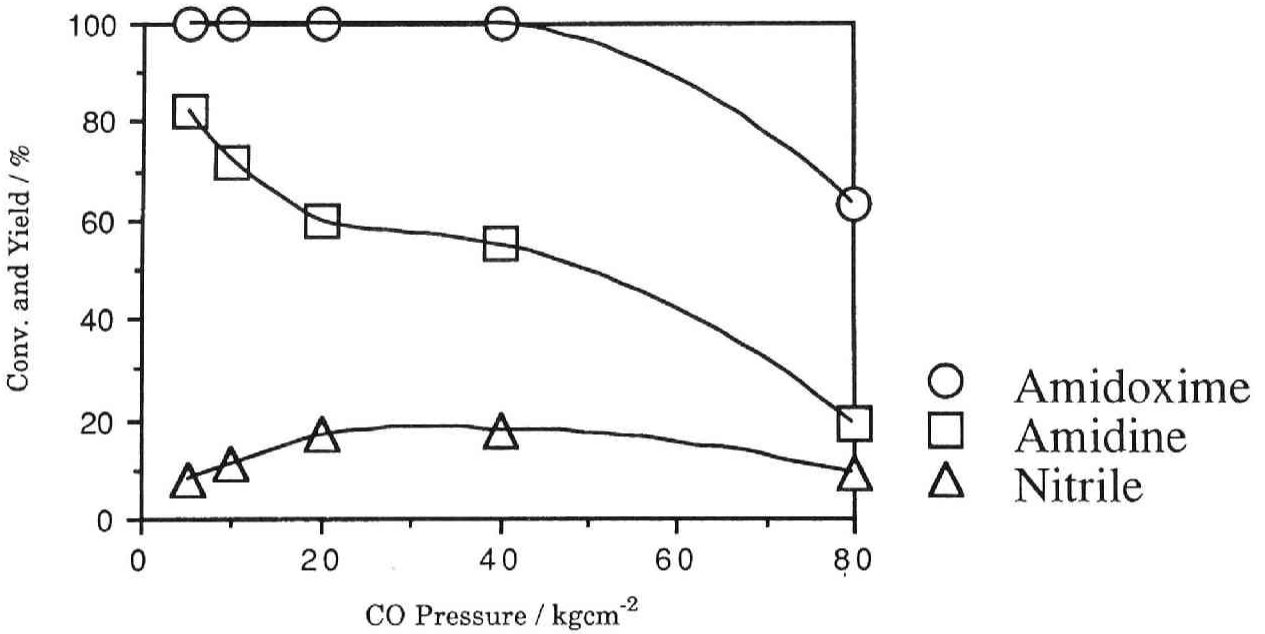
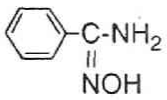
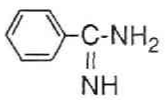
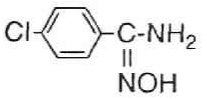
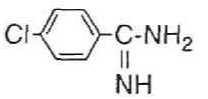
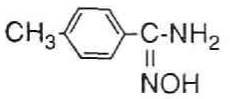
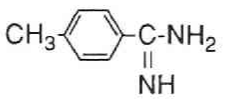
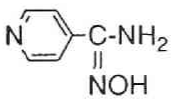
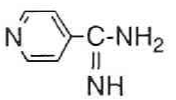
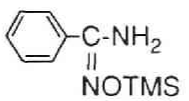


Figure 2. Effect of CO pressure on $Ru_3(CO)_{12}$-catalyzed deoxygenation of benzamidoxime to benzamidine. Reaction conditions: benzaldoxime (5.0 mmol), $Ru_3(CO)_{12}$ (0.10 mmol), THF (5.0 ml) at 80 °C for 4h.

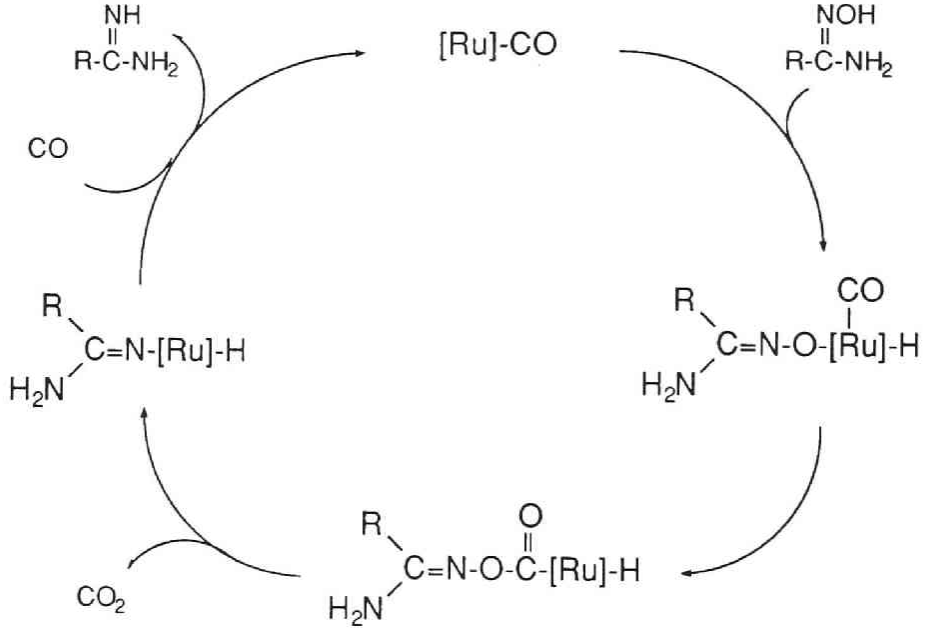
Table II. $Ru_3(CO)_{12}$-Catalyzed Deoxygenation of Aromatic and Heteroaromatic Amidoximes to Amidines[a]

Run	Amidoxime	Product	Yield/%[b]
14			61[c] (82)
15			78
16			72
17			45
18[d]		—	0

a) Amidoxime (5.0 mmol), $Ru_3(CO)_{12}$ (0.10 mmol), THF (5.0 ml) under CO (5 $kgcm^{-2}$) at 80 °C for 5 h. b) Isolated yields (GLC yield).
c) Isolated as benzamidine hydrochloride salt. d) TMS=trimethylsilyl.

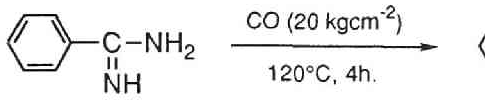
A most plausible catalytic cycle for the present deoxygenation reaction is illustrated in Scheme 1. Firstly, oxidative addition of O-H bond in amidoxime to an active low-valent ruthenium species would proceed in a similar manner of the oxidative addition of alcohols[12] to give the corresponding (amidoximato)ruthenium intermediate. If β-hydrogens exist in the generated complex, β-hydride elimination and/or decomposition of the complex subsequently occur, but the generated amidoximate complex in the present

reaction has no β-hydrogen. Thus, carbon monoxide would migrate into Ru-O bond and the evolution of carbon dioxide affords a hydrido(amido)ruthenium intermediate. Finally, the reductive elimination of the amidine regenerates an active low-valent ruthenium species. Wilkinson et. al. have already reported the synthesis of several stable bis(oximato)ruthenium complexes by the reaction of $RuCl_2(PPh_3)_3$ with oximes and NaOH,[13] and in the present reaction, the generation of the (amidoximato)ruthenium complex seems plausible. In addition, the observation that *O*-substituted amidoximes such as *O*-(trimethylsilyl)benzamidoxime (Run 18) and *O*-methylbenzamidoxime were not converted into the corresponding benzamidines at all, also suggests that the key step of the present reaction is the oxidative addition of amidoximes to an active ruthenium species.



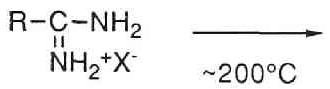
Scheme 1

As for the formation of the nitrile, the ruthenium catalyst also plays some role under the present reaction conditions (eq 3), even though Partridge et al. have reported the thermal decomposition of amidine salts to nitriles at near 200 °C (eq 4).[14]



(3)

	Conv./%	Yield of nitrile/%
$Ru_3(CO)_{12}$ (0.10 mmol)	66	56
no catalyst	21	10

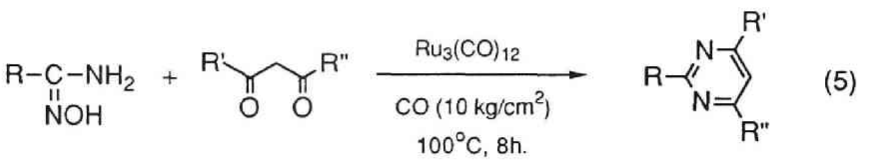


(4)

One-Pot Synthesis of Pyrimidine Derivatives Using Ruthenium-Catalyzed Deoxygenation Reaction of Amidoximes

Among the methods for the synthesis of pyrimidines, Pinner's pyrimidine synthesis, *i.e.*, the condensation reaction of amidines with 1,3-dicarbonyl compounds, is the most well-known and generally employed method,[9] and more recently, the synthesis of pyrimidine 1-oxides by the reaction of amidoximes with C_3 synthons such as 1,1,3,3,-tetramethoxypropane was reported by Polanc et al.[15] In either case, however, it is necessary to operate these reactions under basic[9] or acidic[15] reaction conditions. Thus, we attempted to apply the above mentioned deoxygenation reaction of amidoximes to amidines to one-pot synthesis of pyrimidine

derivatives under neutral reaction conditions. Consequently, when the ruthenium-catalyzed deoxygenation of amidoximes to amidines was carried out in the presence of 1,3-dicarbonyl compounds such as acetylacetone, acetylacetophenone, and ethyl acetoacetate, the subsequent condensation of the generated amidines with 1,3-dicarbonyl compounds smoothly proceeded under neutral reaction conditions to give the corresponding pyrimidine derivatives in good yields (eq 5).

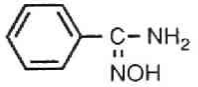
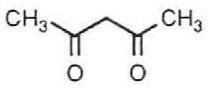
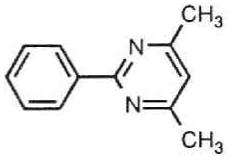
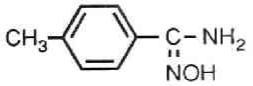
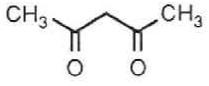
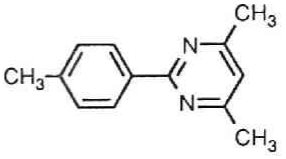
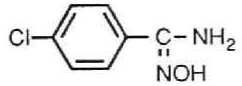
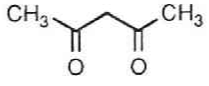
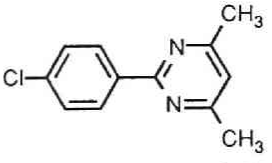
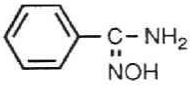
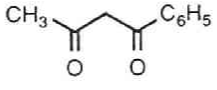
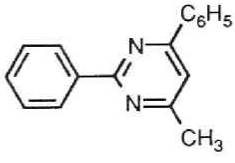
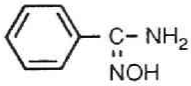
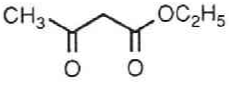
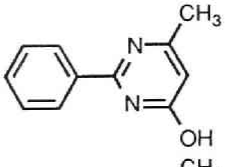
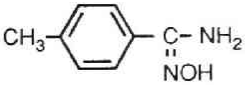
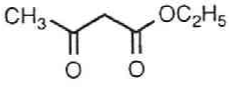
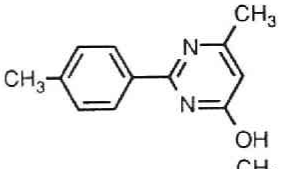
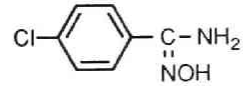
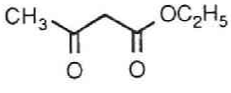
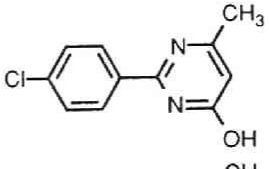
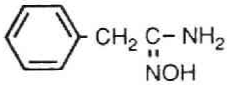
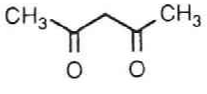
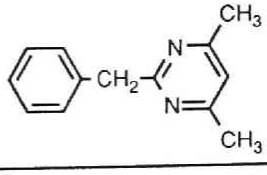


(5)

Results are summarized in Table III. The treatment of aromatic amidoximes with acetylacetone and acetylacetophenone afforded the corresponding pyrimidines in 60-85% yields (Runs 19-22). In the case of ethyl acetoacetate, 4-hydroxypyrimidine was selectively obtained under the present reaction conditions (Runs 23-25).* However, phenylacetoamidoxime, aliphatic amidoximes, reacted with acetylacetone to give 2-benzyl-4,6-dimethyl-pyrimidine in only 33% yield (Run 26), reminiscent of the low reactivity of aliphatic amidoximes in the deoxygenation to the corresponding aliphatic amidines (*vide supra*, eq 2).

Furthermore, in the absence of $Ru_3(CO)_{12}$, benzamidoxime did not react with acetylacetone at all under the present reaction conditions. The ruthenium-catalyzed generation of amidines is essential for the present pyrimidine synthesis.

Table III. One-Pot Synthesis of Pyrimidine Derivatives from Amidoximes and 1,3-Dicarbonyl Compounds[a]

Run	Amidoxime	1,3-Dicarbonyl Compound	Product	/%[b]
19				79
20				85
21				67
22				60
23				93
24				93
25				60
26				33

a) Amidoxime (5.0 mmol), 1,3-dicarbonyl compound (5.5 mmol), $Ru_3(CO)_{12}$ (0.10 mmol), THF (5.0 ml) under CO (10 $kgcm^{-2}$) at 100 °C for 8 h.

b) Isolated yields.

[Experimental Section]

Materials.

The amidoximes were prepared from hydroxylamine and the corresponding nitriles according to the literature's methods.[16] Tetrahydrofuran (THF) was distilled under an argon atmosphere from sodium benzophenone ketyl. Carbon monoxide (>99.9%) was used without further purification. $Ru_3(CO)_{12}$, $Co_2(CO)_8$, and $Mn_2(CO)_{10}$ were purchased from Strem Chemicals; $Ru(acac)_3$ and $RuCl_3 \cdot nH_2O$ (mainly n=3) were purchased from Mitsuwa Chemicals; $Fe(CO)_5$ and $Fe_3(CO)_{12}$ were purchased from Aldrich Chemical Company. They were used without further purification. $Rh_6(CO)_{16}$,[17] $Pd(PPh_3)_4$,[18] $RuCl_2(PPh_3)_3$,[19] and $Ru(CO)_3(PPh_3)_2$[20] were prepared according to the literture's methods.

General procedures.

A 50 ml stainless steel autoclave (Yuasa Giken; SUS 316) was used in all reactions. A glass liner and a magnetic stirring bar were set in the autoclave. A mixture of amidoxime (5.0 mmol), tetrahydrofuran (5.0 ml), and $Ru_3(CO)_{12}$ (0.10 mmol) was placed in it in this order. After sealing and purging with three 10 $kgcm^{-2}$ pressurization depressurization cycles of carbon monoxide, the reactor was pressurized to 5 $kgcm^{-2}$ with carbon monoxide (at room temperature). The autoclave was then heated to 80 °C within 10 min with stirring, and held at this temperature for 5 h. The reaction was terminated by rapid cooling, and gaseous products were discharged (or analyzed in some reactions). The resulting orange solution was analyzed by GLC.

Analytical procedures.

The products were isolated by Kugelrohr distillation. Otherwise, dry HCl gas[21] was passed through the reaction mixture and the generated

amidine hydrochloride salts were collected by filtration. The identification of the products was confirmed by ^{1}H NMR, ^{13}C NMR, FT-IR, GC-MS, and elemental analysis. GLC analyses were performed on a Shimadzu GC-4CM chromatograph with a glass column (3 mm i.d. × 3 m) packed with Apiezon Grease L (5 % on Neopak 1A, 60-80 mesh). Yields of products were determined by the GLC internal standard method. Gaseous products were analyzed by Shimadzu GC-8A chromatograph equipped with thermal conductivity detection (TCD) with a glass column (3 mm i.d. × 3 m) packed with active carbon. ^{1}H NMR spectra were obtained at 89.55 MHz on a JEOL JNM FX-90 spectrometer and ^{13}C NMR spectra at 25.05 MHz with a JEOL JNM FX-100 spectrometer, using $CDCl_3$ or d^6-DMSO as a solvent and tetramethylsilane as an internal standard. IR spectra were measured on a Shimadzu FTIR 8100 spectrophotometer. Mass spectra were obtained on a Shimadzu QP2000 spectrometer. Elemental analyses were performed at the Microanalytical Center of Kyoto University. The analytical data of the representative products are described below.

Benzamidine hydrochloride: white solid; mp 169 °C; ^{1}H NMR (d^6DMSO): δ 7.58-8.04 (m, 5H, phenyl), 9.51 (br, 4H, -NH_2 and =$NH_2^+Cl^-$); ^{13}C NMR (d^6DMSO): δ 127.6 (s, phenyl), 127.9 (d, phenyl), 128.8 (d, phenyl), 133.6 (d, phenyl), 165.6 (s, C=N); IR (KBr): 3320 (br, ν_{N-H}), 1678 (s, $\nu_{C=N}$) cm^{-1}.

4-Methylbenzamidine: white solid; bp 200°C/1mmHg(Kugelrohr distillation); ^{1}H NMR (d^6DMSO): δ 2.31(s, 3H, -CH_3), 6.06(br, 3H, -NH_2, =NH), 7.18 (d, 2H, phenyl, J=8.0 Hz), 7.71 (d, 2H, phenyl, J=8.0 Hz); ^{13}C NMR (d^6DMSO): δ 20.7 (q, -CH_3), 126.3 (d, phenyl), 128.5 (d, phenyl), 133.6 (s, phenyl), 139.1 (s, phenyl), 162.7 (s, C=N); IR (KBr): 3230 (br, ν_{N-H}), 1632 (s, $\nu_{C=N}$) cm^{-1}; MS m/z 134 (M^+);

Anal. calcd. for $C_8H_{10}N_2$: C, 71.61; H, 7.51, N; 20.88. Found: C, 71.66; H, 7.44; N, 20.73.

4,6-Dimethyl-2-phenylpyrimidine: white solid; mp 82.4-83.0 °C; ^{1}H NMR ($CDCl_3$): δ 2.45 (s, 6H, -C*H*$_3$), 6.80 (s, 1H, pyrimidineC5-*H*), 7.28-7.55 (m, 3H, phenyl), 8.31-8.51 (m, 2H, phenyl); ^{13}C NMR ($CDCl_3$): δ 24.1(q, -*C*H$_3$), 117.8 (d, pyrimidine*C*5), 128.2 (d, phenyl), 128.3 (d, phenyl), 130.2 (d, phenyl), 138.0 (s, phenyl), 164.0 (s, pyrimidine*C*2), 166.6 (s, pyrimidine*C*4 and *C*6); MS 184 (M^+, 100), 169 (21.2), 104 (37.2), 103 (47.6); Anal. calcd. for $C_{12}H_{12}N_2$; C, 78.23; H, 6.56; N, 15.21. Found C, 78.05; H, 6.44; N, 15.18.

2-(4-Methylphenyl)-4,6-dimethylpyrimidine: white solid; mp 139.0-139.5 °C; ^{1}H NMR ($CDCl_3$): δ 2.37 (s, 3H, -C_6H_4C*H*$_3$), 2.47 (s, 6H, pyrimidineC*H*$_3$), 6.80 (s, 1H, pyrimidineC5-*H*), 7.24 (d, 2H, phenyl, *J*= 8.0Hz), 8.32 (d, 2H, phenyl, *J*= 8.0Hz); ^{13}C NMR ($CDCl_3$): δ 23.3 (q, -C_6H_4*C*H$_3$), 24.0 (q, pyrimidine*C*H$_3$), 117.2 (d, pyrimidine*C*5), 127.9 (d, phenyl), 128.8 (d, phenyl), 135.1 (s, phenyl), 140.0 (s, phenyl), 163.6 (s, pyrimidine*C*2), 166.1 (s, pyrimidine*C*4 and *C*6); MS 198 (M^+, 100), 197 (M^+-1, 32.2), 117 (24.3); Anal. calcd. for $C_{13}H_{14}N_2$. C, 78.75; H, 7.12; N, 14.13. Found: C, 78.59: H, 7.05: N, 14.12.

2-(4-Chlorophenyl)-4,6-dimethylpyrimidine: white solid; bp 210 °C / 0.5 mHg (Kugelrohr distillation); ^{1}H NMR ($CDCl_3$): δ 2.47 (s, 6H, -C*H*$_3$), 6.83(s, 1H, pyrimidineC5-*H*), 7.39(d, 2H, phenyl, *J*= 9Hz), 8.37(d, 2H, phenyl, J= 9Hz); ^{13}C NMR ($CDCl_3$): δ 24.1(q, -*C*H$_3$), 118(d, pyrimidine*C*5), 128.5(d, phenyl), 129.6(d, phenyl), 136.4(s, phenyl), 136.6(s, phenyl), 162.9(s, pyrimidine*C*2), 166.7(s, pyrimidine*C*4); MS 220(M[^{37}Cl]$^+$, 30.7), 218(M[^{35}Cl]$^+$, 100), 138(21.1), 137(38.3).

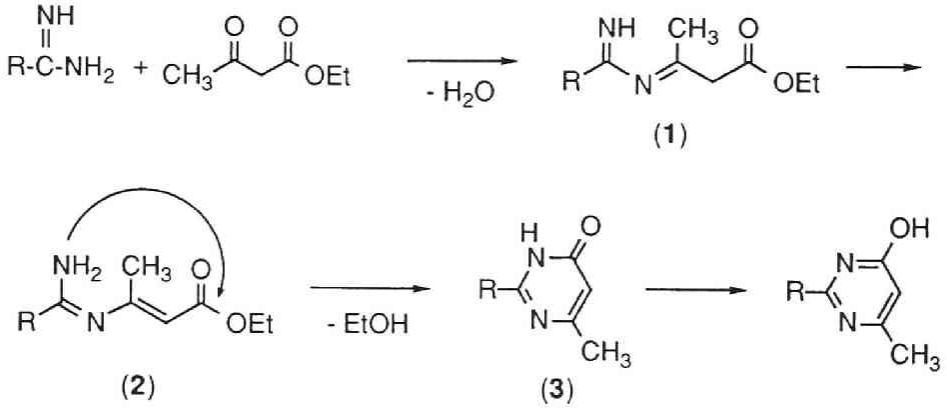
4-Methyl-2,6-diphenylpyrimidine: white solid; bp 240 °C / 0.1 mmHg(Kugelrohr distillation); ^{1}H NMR ($CDCl_3$): δ 2.60(s, 3H, -C*H*$_3$), 7.33-7.55(m, 7H, phenyl, pyrimidineC5-*H*), 8.13-8.23(m, 2H, phenyl), 8.53-8.64(m, 2H, phenyl); ^{13}C NMR ($CDCl_3$): δ 24.6(q, -CH3), 113.9(d, pyrimidine*C*5), 127.1(d, phenyl), 128.4(d, phenyl), 128.7(d, phenyl), 130.4(d, phenyl), 130.5(d, phenyl), 137.2(s, phenyl), 138.1(s, phenyl), 163.6(s, pyrimidine), 164.2(s, pyrimidine), 167.6(s, pyrimidine); MS 246(M+, 100), 143(39.1), 102(45.5).

4-Hydroxy-6-methyl-2-(4-methylphenyl)-pyrimidine: white solid; mp 222.5-223.0 °C; ^{1}H NMR ($CDCl_3$): δ 2.34 (s, 3H, phenylC*H*$_3$), 2.38 (s, 3H, pyrimidineC*H*$_3$), 6.23 (s, 1H, pyrimidineC5-*H*), 7.28 (d, 2H, phenyl, *J*=8.0Hz), 8.07 (d, 2H, phenyl, *J*=8.0Hz), 10.71 (br, 1H, -O*H*); ^{13}C NMR ($CDCl_3$): δ 21.4 (q, phenyl*C*H$_3$), 24.1 (q, pyrimidine*C*H$_3$), 110.3 (d, pyrimidine*C*5), 127.8 (d, phenyl), 129.4 (d, phenyl), 129.8 (s, phenyl), 142.1 (s, phenyl), 157.0 (s, pyrimidine), 165.8 (s, pyrimidine), 166.1 (s, pyrimidine); Anal. calcd. for $C_{12}H_{12}N_2O$: C, 71.98; H, 5.60;.N, 13.99. Found: C, 71.70; H, 5.95; N, 14.10.

2-Benzyl-4,6-dimethylpyrimidine: white solid; bp 155 °C / 0.35 mmHg (Kugelrohr distillation); ^{1}H NMR ($CDCl_3$): δ 2.42(s, 6H, -C*H*$_3$), 4.20(s, 2H, -C*H*$_2$-), 6.82(s, 1H, pyrimidineC5-*H*), 7.24-7.39(m, 5H, phenyl); ^{13}C NMR ($CDCl_3$): δ 23.98(q, 2C, -CH3), 45.93(t, -CH2-), 117.57(d, pyrimidine*C*5), 126.30(d, phenyl), 128.30(d, phenyl), 129.05(d, phenyl), 138.71(s, phenyl), 166.78(s, pyrimidine *C*4,*C*6), 168.93(s, pyrimidne*C*2).

[Footnote]

*The reason that 4-hydroxypyrimidine instead of 4-ethoxypyrimidine was mainly obtained in the present reaction, is explained by the following mechanism (Scheme 2). Firstly, condensation of amino group in amidine with keto-carbonyl group of ethyl acetoacetate via dehydration would occur. Isomerization of intermediate (**1**) to (**2**) subsequently proceeds and the generated amino group in (**2**) would be acylated by ester functionality[22] to give (**3**), followed by the further isomerization to afford 4-hydroxypyrimidine selectively.



Scheme 2

[References]

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Chapter 7

Ruthenium Complex-Catalyzed Deoxygenative Allylation of Aldoximes by Allylic Carbonates: Novel Synthesis of Homoallylic Amines

[Summary]

Several ruthenium complexes show a high catalytic activity for the deoxygenative allylation of a carbon-nitrogen double bond in aldoximes with various allylic carbonates via deoxygenation of aldoximes under carbon monoxide pressure to give homoallylic amines in moderate to good yields. In the presence of a catalytic amount of $Ru_3(CO)_{12}$, the reaction of 4-methoxylbenzaldoxime with allyl methyl carbonate afforded *N*-(4-methoxybenzylidene)-1-(4-methoxyphenyl)-3-buten-1-amine in 74% yield. This reaction is the first example of the *true catalytic* allylation of a carbon-nitrogen double bond.

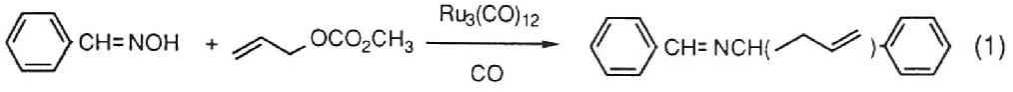
[Introduction]

Due to the importance of carbonyl allylation reaction for selective carbon-carbon bond forming reactions, allylic alkylation of aldehydes and ketones using various allylic reagents has been extensively studied and successfully applied in organic synthesis.[1] In the field of transition-metal complex catalysis, allylation of carbonucleophiles by π-allylpalladium complexes has been fully investigated and has become a powerful tool for organic synthesis.[2]

Recently, much attention has been paid for the umpolung of electrophilic π-allylpalladium intermediate using zinc,[3] tin,[4] or samarium[5] as a reducing reagent and subsequent nucleophilic allylation of aldehydes or ketones can be explored. Furthermore, the examples of allylation of a carbon-nitrogen double bond are strictly limited compared with the carbonyl allylation. Almost all of these examples reported until now require a stoichiometric amount of allylic lithium,[7] magnesium,[8] borane,[9] and tin,[10] and catalytic allylation of a carbon-nitrogen double bond has not yet been reported. In the course of our study on ruthenium complex-catalysis,[11] we have recently reported the first example of ruthenium-catalyzed allylation of aldehydes by allylic acetates to homoallylic alcohols[12a] and dehydrogenative allylation of primary alcohols by allylic acetates to α,β-unsaturated ketones.[12b] In these reactions, π-allyl moiety of the possible π-allylruthenium intermediate apparently functioned as a nucleophile rather than as an electrophile and these reactions smoothly proceeded without an use of another metal such as SmI_2 or $SnCl_2$ for umpolung.

In this chapter, we succeeded in further developing this novel reactivity of π-allylruthenium intermediates and on the basis of ruthenium-catalyzed highly selective deoxygenation reactions of ketoximes and amidoximes to the corresponding imines, we now disclose the deoxygenative allylation of

aldoximes to homoallylic amines catalyzed by low valent ruthenium complexes. This reaction is the first example of *true catalytic* allylation of carbon-nitrogen double bonds. For example, *N*-benzylidene-1-phenyl-3-buten-1-amine was obtained from the reaction of benzaldoxime with allyl methyl carbonate (eq 1)



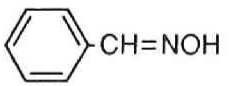
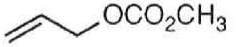
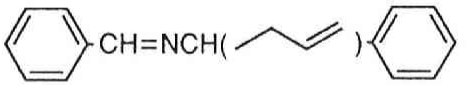
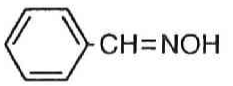
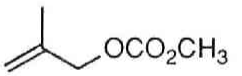
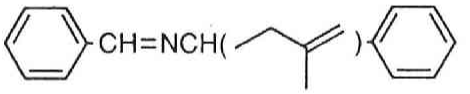
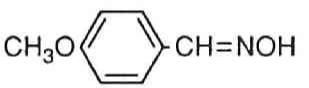
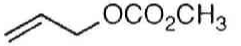
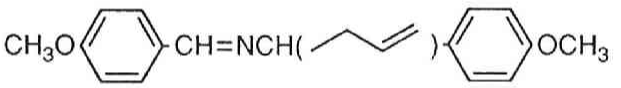
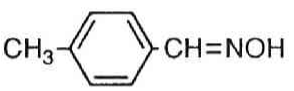
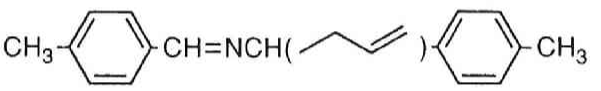
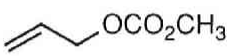
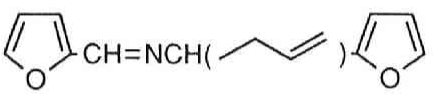
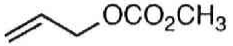
(1)

[Results and Discussion]

Ruthenium-Catalyzed Deoxygenative Allylation of a Carbon-Nitrogen Double Bond of Aldoximes; Novel Synthesis of Homoallylic Amines

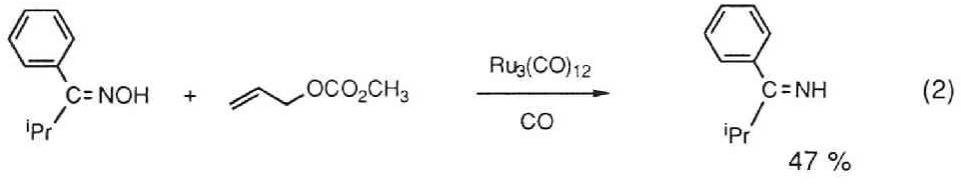
Aromatic and aliphatic aldoximes are smoothly deoxygenated and allylated by allylic carbonates in the presence of a catalytic amount of $Ru_3(CO)_{12}$ under 10 $kgcm^{-2}$ of initial carbon monoxide pressure to give the corresponding homoallylic amines in moderate to good yields. Results are summarized in Table I. For example, the deoxygenative allylation of 4-methoxybenzaldoxime by allyl methyl carbonate afforded the corresponding homoallylic amine in 74% yield (Run 3). On the other hand, the deoxygenative allylation of aliphatic aldoximes gave the corresponding homoallylic amines in low yield, since the general aliphatic homoallylic amines were not so stable under the present reaction conditions and gradually transformed to high boiling products (Run 6).

Table I. Ruthenium-Catalyzed Deoxgenative Allylation of Aldoximes by Allylic Carbonates[a]

Run	Aldoxime	Allylic carbonate	Product	Yield / %[b]
1				45 (47)
2				60 (61)
3				74
4				63
5				63
6				37

a) Aldoxime (3.3 mmol), allylic carbonate (20 mmol), $Ru_3(CO)_{12}$ (0.10 mmol), THF (8.0 ml) under CO (10 $kgcm^{-2}$) at 120 °C for 6h. b) Isolated yields (GLC yields).

The present allylation reaction is chemoselective to aldoximes. As for ketoximes such as 3-pentanone oxime, methyl phenyl ketoxime and isopropyl phenyl ketoxime, the present allylation did not proceed at all. In the reaction with isopropyl phenyl ketoxime, only the deoxygenation of ketoxime proceeded to give isopropyl phenyl ketimine in 47% isolated yield (eq 2). A similar chemoselectivity was observed in our previously reported ruthenium-catalyzed allylation of aldehydes, in which allylation of ketones did not proceed at all.[12]



(2)

Catalytic activities of several transition-metal complexes were examined in the deoxygenative allylation of benzaldoxime by allyl methyl carbonate. Results are summarized in Table II. Among the catalyses examined, zerovalent ruthenium complexes such as $Ru_3(CO)_{12}$, Ru(COD)(COT) and $Ru(CO)_3(PPh_3)_2$ generally showed high catalytic activity (Runs 1, 7, and 8). Under carbon monoxide pressure, Ru(COD)(COT) was readily converted into the ruthenium carbonyl species.[11c] On the other hand, the catalytic activity of divalent ruthenium complexes such as $RuCl_2(PPh_3)_3$ was quite low (Run 9), but the concomitant use of $RuCl_2(PPh_3)_3$ with K_2CO_3 drastically increased the catalytic activity and the yield of the homoallylic amine reached up to 43% (Run 10). This result suggests that divalent ruthenium complexes would be reduced to zerovalent ones under the present conditions and an active catalyst species would be zerovalent ruthenium complexes. In addition, other group VII and VIII transition-metal carbonyl complexes were almost ineffective in the present reaction (Runs 11-14).

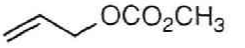
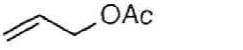
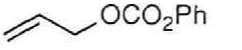
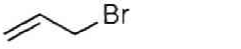
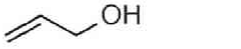
Table II. Catalytic Activities of Several Transition-Metal Complexes[a]

Run	Catalyst	Yield/%[b]
1	$Ru_3(CO)_{12}$	45 (47)
7	Ru(COD)(COT)	44
8	$Ru(CO)_3(PPh_3)_2$	40
9	$RuCl_2(PPh_3)_3$	7
10[c]	$RuCl_2(PPh_3)_3$	43
11	$Rh_6(CO)_{16}$	8
12	$Mn_2(CO)_{10}$	0
13	$Fe_3(CO)_{12}$	0
14	$Co_2(CO)_8$	0

a) Benzaldoxime (3.3 mmol), allyl methyl carbonate (20 mmol), catalyst (0.10 mmol), THF (8.0 ml) under CO (10 $kgcm^{-2}$) at 120 °C for 6 h. b) GLC yields (Isolated yield). c) K_2CO_3 (5.0 mmol) was added.

The effect of leaving groups of allylic compounds was examined in the deoxygenative allylation of benzaldoxime, and the results are summarized in Table III. Both allyl methyl carbonate and allyl acetate smoothly reacted with aldoximes to give the corresponding homoallylic amine in good yields (Runs 1 and 15). However, allyl phenyl carbonate also afforded the corresponding homoallylic amine but the yield was relatively low (28%; Run 16), and other allylic compounds such as allyl bromide, allyl chloride and allyl alcohol were totally ineffective (Runs 17-19).

Table III. Effect of Leaving Groups of Several Allylic Compounds[a]

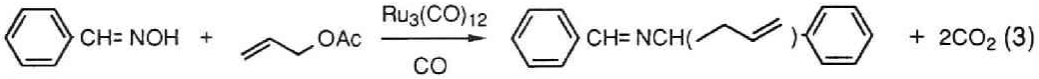
Run	Allylic compound	Yield / %[b]
1		47 (45)
15		44
16		28
17		6
18		1
19		0

a) Benzaldoxime (3.3 mmol), allylic compound (20 mmol), THF (8.0 ml), $Ru_3(CO)_{12}$ (0.10 mmol) under CO (10 $kgcm^{-2}$) at 120 °C for 6 h. b) GLC yields (Isolated yield).

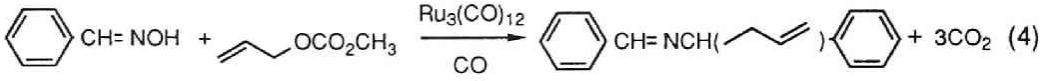
The Analysis of Gas Phase after the Reaction and Roles of Carbon Monoxide

After the reaction of runs 1 and 15, carbon dioxide was detected in a gas phase (eqs 3 and 4). In the deoxygenative allylation of benzaldoxime with allyl acetate, the corresponding homoallylic amine was obtained in 44% yield,

together with twice amount of carbon dioxide as much as the amount of homoallylic amine (eq 3). In the use of allyl methyl carbonate, the amine was obtained in 47% yield, together with three times amount of carbon monoxide as much as the amount of the product (eq 4). These results suggest that twice amount of carbon dioxide was generated from the formation of one molecule of homoallylic amine. In the reaction with allylic carbonate, one molecule of carbon dioxide was generated from one molecule of allylic carbonate and the total amount of carbon dioxide should be three times as much as that of the amine.

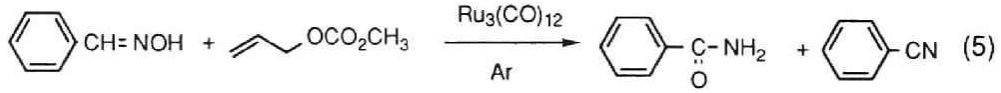


44 %



47 %

In the absence of carbon monoxide, i.e., under an argon atmosphere, the allylation reaction did not proceed at all and a mixture of benzamide (54 % yield) and benzonitrile (32 % yield) was obtained as products (eq 5). Isomerization of aldoximes to amides using nickel acetate[13] has already been reported and dehydration of aldoximes to nitriles by transition-metal complexes was also reported by Kaneda et al.[14] and by our previous work.[15] Thus carbon monoxide is essential for the present reaction to inhibit the side reactions such as isomerization and dehydration of aldoximes, as well as to stabilize an active ruthenium species.



54 % 32 %

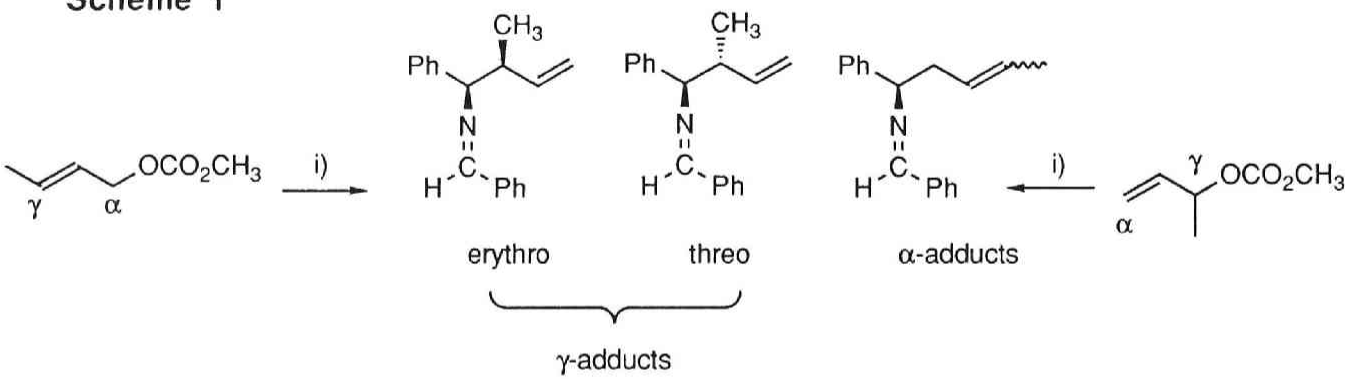
Regioselectivity and Diastereoselectivity in the Deoxygenative Allylation of Aldoximes

The results of regio- and diastereoselectivity of the products obtained from the reaction of (E)-crotyl carbonate and 3-buten-2-yl methyl carbonate with benzaldoxime are shown in Scheme 1. Since almost the same regio- and diastereoselectivity were observed in both reactions especially in DMI (*N,N'*-dimethylimidazolone), the reaction would proceed via a common π-allylruthenium intermediate. The relatively high selectivity of α-adducts is an unusual example, since both stoichiometric allylation of carbonyl compounds using allylic metal reagents and catalytic allylation reactions reported by us[12] generally occur at a more sterically hindered position of an allylic moiety. As for solvent effects, Masuyama et al. reported that their carbonyl allylation by $PdCl_2(PhCN)_2$-$SnCl_2$ system in DMI offered a high γ-regioselectivity.[5d] In the present reaction, however, extremely reverse selectivity was observed and the the α-adduct was obtained as a major product. The reasons of this solvent effect are not clear yet, but both the coordination ability and steric effect of solvents probably have a great influence on the reactivity of the π-allylruthenium intermediate.

Palladium Complex-Catalyzed Selective O-Allylation of Aldoximes

When a palladium catalyst instead of a ruthenium catalyst was employed in the reaction of benzaldoxime with allyl methyl carbonate, the selective *O*-allylation of aldoximes smoothly proceeded, and the corresponding *O*-allylated benzaldoxime was obtained in 70% yield (eq 6). $Pt(PPh_3)_4$ also catalyzed the *O*-allylation of aldoxime but the yield of the product was rather low (28% yield).

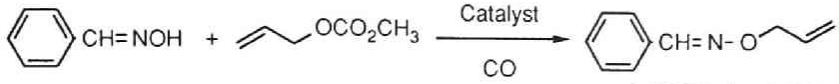
Scheme 1



solvent	erythro : threo : α-adducts
benzene	24 : 10 : 66 (Total 53 %)
THF	31 : 26 : 43 (Total 54 %)
DMI	14 : 6 : 80 (Total 42 %)

solvent	erythro : threo : α-adducts
benzene	27 : 19 : 54 (Total 49 %)
THF	21 : 7 : 72 (Total 45 %)
DMI	12 : 6 : 82 (Total 38 %)

i) Reaction conditions: benzaldoxime (3.3 mmol), allylic compound (20 mmol), solvent (8.0 ml), $Ru_3(CO)_{12}$ (0.10 mmol) under CO (10 $kgcm^{-2}$) at 120 °C for 6 h.
THF = tetrahydrofuran, DMI = *N,N'*-dimethylimidazolone.



(6)

$Pd(PPh_3)_4$: 70%
$Pt(PPh_3)_4$: 28%

In general, *O*-alkylation of oximes with alkyl halides competes with *N*-alkylation of oximes and a mixture of *O*-alkylated oximes and nitrones is obtained (eq 7).[16] Thus, it has been difficult to control the selectivity between *O*-alkylation and *N*-alkylation of oximes in the former reactions. We now consider that the present selective *O*-allylation of oximes is accomplished by using a high electrophilicity of π-allylpalladium intermediates[2] and the reaction offers a novel method for selective *O*-allylation of aldoximes. A similar reaction of oximes with butadiene has been reported by Backer et al., in which they also explained the mechanism by assuming a nucleophilic addition of oximes to an electrophilic π-allylpalladium intermediate derived from butadiene.[17]

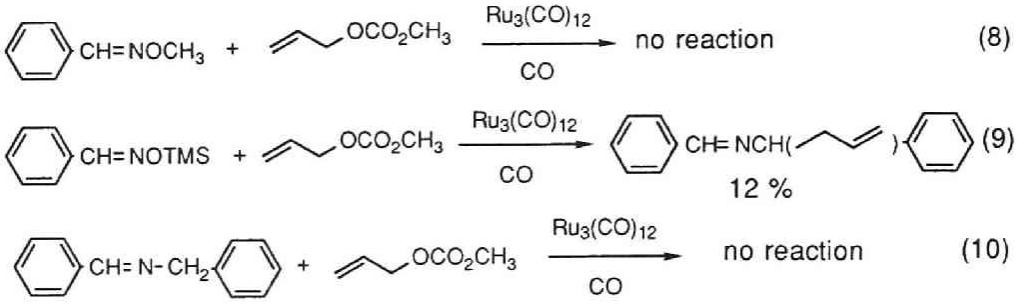
(7)

Mechanistic Study on the Deoxygenative Allylation of Aldoximes

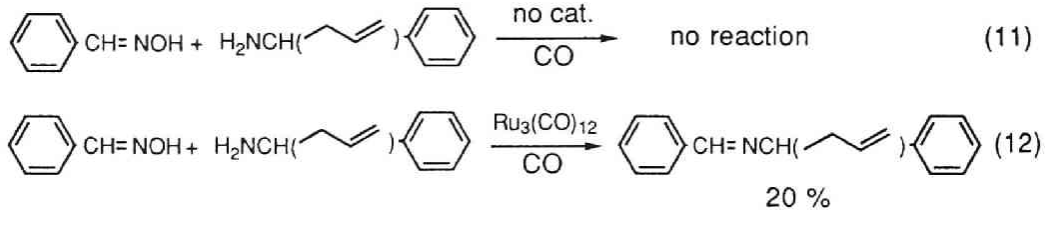
The present deoxygenative allylation of aldoximes is thought to be constructed by deoxygenation of aldoximes, nucleophilic allylation of the C=N bond in the generated aldimines, and condensation of the generated homoallylic amine with another molecule of aldimine. In confirmation of this speculation, we investigated the following reactions.

When *O*-substituted aldoximes such as *O*-methyl benzaldoxime were employed in the present reaction, neither deoxygenation of aldoximes nor allylation of a C=N bond did not proceed at all (eq 8). In the reaction using *O*-trimethylsilyl benzaldoxime, the corresponding homoallylic amine was obtained in only 12% yield, probably via some hydrolysis of *O*-trimethylsilyl

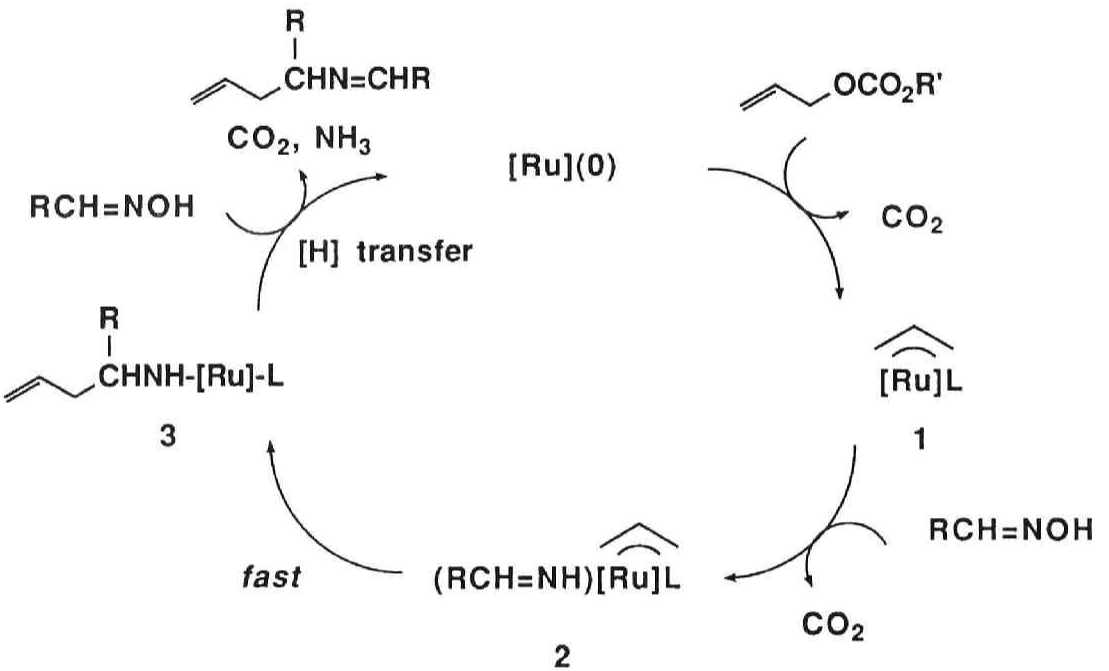
benzaldoxime (eq 9). Furthermore, *N*-benzylidenebenzylamine was not allylated at all under the present reaction conditions (eq 10).



These results suggest that the hydroxyl group in aldoximes is essential for the present reaction, and the first step of the present reaction is an oxidative addition of an O-H bond in aldoximes to an active ruthenium species. In consideration of the result of eq 10, final condensation could proceed after the allylation of a C=N bond. Furthermore, in order to investigate the final condensation process, a homoallylic amine (1-phenyl-3-buten-1-amine) was separately prepared according to the method in the literature,[24b,c] and employed in the reaction with benzaldoxime. In the presence of the ruthenium catalyst and under carbon monoxide pressure (10 $kgcm^{-2}$), 1-phenyl-3-buten-1-amine reacted with benzaldoxime to give the corresponding homoallylic amine in 20% yield (eq 11). However, in the absence of the ruthenium catalyst, both substrates were not converted at all and the condensation between them was totally inhibited (eq 12). These results suggest that the generated homoallylic amine should condense with the aldimine, not with the parent aldoxime.



On the basis of the mechanistic studies described above, a plausible reaction pathway for the present reaction is illustrated in Scheme 2. Ligands on ruthenium (CO or phosphine) are omitted for clarity. Firstly, allylic carbonate or allylic acetate oxidatively adds to an active low valent ruthenium species with the generation of CO_2 to afford a π-allylruthenium intermediate **1**. Then, deoxygenation of aldoxime by **1** using carbon monoxide occurs to give the corresponding aldimine complex **2**. Although free *N*-nonsubstituted aldimines are generally unstable and hardly isolated, they would be stabilized by the coordination to a ruthenium. Indeed, Faller et al. have succeeded in synthesizing an aldimine-coordinated ruthenium complex, $[CpRu(PPh_3)_2(HN{=}CHPh)]PF_6$, and identify its structure by X-ray crystallography.[18] Subsequently, an insertion of the coordinated aldimine into an allyl(π- or σ-)-ruthenium bond generates the (homoallylamido)ruthenium intermediate **3**. Finally, the homoallylic amine, which seems to be obtained by hydrogen transfer reaction from aldoximes and/or allylic compounds, condenses with another molecule of the generated aldimine to afford the product and the active ruthenium species can be regenerated.


R
CHN=CHR
CO2, NH3
RCH=NOH
[H] transfer
[Ru](0)
OCO2R'
CO2
R
CHNH-[Ru]-L
3
[Ru]L
1
RCH=NOH
fast
(RCH=NH)[Ru]L
2
CO2

Scheme 2

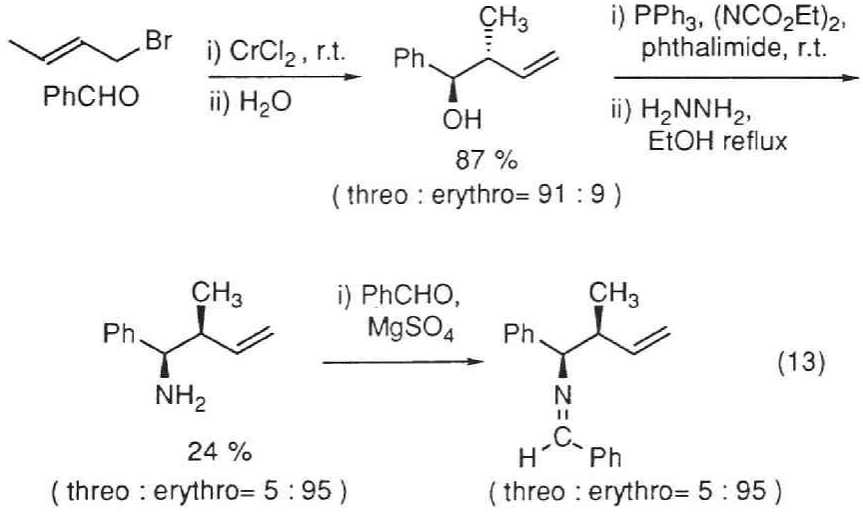
[Experimental Section]

Materials.

The reagents employed in this study were dried and purified before use by the usual procedures. Oximes were prepared by usual methods. Carbon monoxide (>99.9%) was used without further purification. $Ru(COD)(COT)$,[19] $Ru(CO)_3(PPh_3)_2$,[20] $RuCl_2(PPh_3)_3$,[21] and $Rh_6(CO)_{16}$[22] were prepared by the literature methods. $Ru_3(CO)_{12}$, $Mn_2(CO)_{10}$, $Fe_3(CO)_{12}$, and $Co_2(CO)_8$ were purchased from Strem Chemicals and were used without further purification. Only $Co_2(CO)_8$ was recrystallized from n-pentane before use. Authentic sample of *N*-benzylidene-1-phenyl-3-butene-1-amine was prepared by the literature method.[23]

Assignment of Stereochemistry of the Products.

The stereochemistry of *N*-benzylidene-2-methyl-1-phenyl-3-buten-1-amine was identified by comparison of their spectral data with those of the separately synthesized samples (eq 13).[24b,c]



General Procedures.

A mixture of aldoxime (3.3 mmol), allylic carbonate (20 mmol), $Ru_3(CO)_{12}$ (0.10 mmol), and THF (8.0 ml) was placed in a 50-ml stainless steel autoclave (Yuasa Giken; SUS 316) equipped with a glass liner and a magnetic stirring bar. The unit was sealed and then purged three times with 10 $kgcm^{-2}$ pressurization-depressurization cycles of carbon monoxide (at room temperature), and heated for 6 h. The reaction was terminated by rapid cooling, and gaseous products were discharged. The resulting yellow solution was analyzed by GLC and FT-IR. All products were isolated by Kugelrohr distillation. The identification of the products was confirmed by ^1H and ^{13}C-NMR, and GC-MS.

The GLC analyses were carried out on a Shimadzu GC-8A chromatograph equipped with columns (3 m i.d.x 3 m) packed with Silicone OV-17 (2% on Chromosorb W(AW-DMCS), 80-100 mesh)

The IR spectra were measured on a Shimadzu FTIR-8100.

The ^1H-NMR spectra were recorded on a JEOL GSX-270 spectrometer (270 MHz). ^{13}C-NMR spectra were recorded at 25.05 MHz with JEOL JNM FX-100 or at 67.8 MHz with JEOL GSX-270 spectrometer. Samples were dissolved in $CDCl_3$ and the chemical shift values were expressed in relative to Me_4Si as an internal standard.

Mass spectra (MS) were obtained on a Shimadzu QP-2000 spectrometer.

Spectroscopic data of the representative products were shown below.

***N*-Benzylidene-1-phenyl-3-buten-1-amine**: colorless liquid; 170 °C/ 0.2 mmHg(Kugelrohr distillation); IR(neat) 1646 cm^{-1} ($\nu_{C=N}$); ^1H-NMR($CDCl_3$) δ 2.69(t, 2H, -C*H*$_2$-, J=6.9Hz), 4.33(t, 1H, -NC*H*-, J=6.9Hz), 4.98-5.07(m, 2H, =C*H*$_2$), 5.64-5.79(m, 1H, -C*H*=), 7.17-7.79(m, 10H, phenyl), 8.27(s, 1H, -C*H*=N-); ^{13}C-

NMR($CDCl_3$) δ 43.14(t, -*C*H2-), 68.03(d, -N*C*H-), 117.17(t, =*C*H_2), 126.96(d, phenyl), 127.03(d, phenyl), 128.28(d, phenyl), 128.37(d, phenyl), 128.46(d, phenyl), 130.53(d, phenyl), 135.41(d, -*C*H=), 136.27(s, phenyl), 143.81(s, phenyl), 143.81(s, phenyl), 159.98(d, -*C*H=N-), mass spectrum (electron impact) m/e 235(M^+, 1.3), 194(M^+-C_3H_5, base peak).

***N*-Benzylidene-3-methyl-1-phenyl-3-buten-1-amine**: colorless liquid; 150 °C / 0.2 mmHg(Kugelrohr distillation); IR(neat) 1646 cm^{-1} ($\nu_{C=N}$); ^{1}H-NMR($CDCl_3$) δ 1.72(s, 3H, -C*H*$_3$), 2.56-2.71(m, 2H, -C*H*$_2$-), 4.42-4.47(m, 1H, -NC*H*-), 4.66-4.75(m, 2H, =C*H*$_2$), 7.19-7.78(m, 10H, phenyl), 8.24(s, 1H, -C*H*=N-); ^{13}C-NMR($CDCl_3$) δ 23.1(q, -*C*H_3), 47.0(t, -*C*H_2-), 73.8(d, -N*C*H-), 113.3(t, =*C*H_2), 126.8(d, phenyl), 128.1(d, phenyl), 128.2 (d, phenyl), 136.1(s, =*C*=), 142.0(s, phenyl), 143.8(s, phenyl), 159.3(d, -*C*H=N-).

***N*-Benzylidene-2-methyl-1-phenyl-3-buten-1-amine (erythro)**: colorless liquid; 170 °C/0.2 mmHg(Kugelrohr distillation); IR(neat) 1646 cm^{-1} ($\nu_{C=N}$); ^{1}H-NMR($CDCl_3$) δ 1.03(d, 3H, -C*H*$_3$, J=6.8Hz), 2.81(dq, 1H, -C*H*CH_3, J=6.8, 7.0Hz), 4.07(d, 1H, -NC*H*-, J=7.3Hz), 4.89-4.95(m, 2H, =C*H*$_2$), 5.63-5,76(m, 1H, -C*H*=), 7.19-7.42(m, 8H, phenyl), 7.75-7.78(m, 2H, phenyl), 8.25(s, 1H, -C*H*=N-); ^{13}C-NMR($CDCl_3$) δ 16.06(q, -*C*H_3), 44.72(d, -*C*HCH3), 80.49(d, -N*C*H-), 114.64(t, =*C*H_2), 126.77(d, phenyl), 127.75(d, phenyl), 128.06(d, phenyl), 128.26(d, phenyl), 128.44(d, phenyl), 130.46(d, phenyl), 136.38(s, phenyl), 141.26(d, -*C*H=), 143.15(s, phenyl), 159.94(d, -*C*H=N-).

***N*-(4-Methylbenzylidene)-1-(4-methylphenyl)-3-buten-1-amine**: colorless liquid; 230 °C/0.3 mmHg(Kugelrohr distillation); IR(neat) 1646 cm^{-1} ($\nu_{C=N}$); ^{1}H-NMR($CDCl_3$) δ 2.29(s, 3H, -C*H*$_3$), 2.32(s, 3H, -C*H*$_3$), 2.67(m, 2H, -C*H*$_2$-), 4.28(t, 1H, -NC*H*-, J=6.8Hz), 4.95-5.06(m, 2H, =C*H*$_2$), 5.66-5.79(m, 1H, -C*H*=), 7.12(d,

2H, phenyl, J=8.1Hz), 7.15(d, 2H, phenyl, J=8.1Hz), 7.31(d, 2H, phenyl, J=8.1Hz), 7.64(d, 2H, phenyl, J=8.1Hz); ^{13}C-NMR($CDCl_3$) δ 21.03(q, -*C*H_3), 21.42(q, -*C*H_3), 43.09(t, -*C*H_2-), 116.95(t, =*C*H_2), 126.94(d, phenyl), 128.26(d, phenyl), 129.03(d, phenyl), 129.16(d, phenyl), 133.78(s, phenyl), 135.63(d, -*C*H=), 136.36(s, phenyl), 140.64(s, phenyl), 140.95(s, phenyl), 159.71(d, -*C*H=N-), MS, m/z(relative intensity) 263(M^+, 1.1), 222(M^+-C_3H_5, 100).

***N*-(4-Methoxybenzylidene)-1-(4-methoxyphenyl)-3-butene-1-amine**: colorless liquid; 250 °C/0.15 mmHg(Kugelrohr distillation); ^{1}H-NMR($CDCl_3$) δ 2.65(t, 2H, -C*H*$_2$-, J=7.1Hz), 3.74(s, 6H, -C*H*$_3$), 4.25(t, 1H, -NC*H*-, J=6.8Hz), 4.95-5.06(m, 2H,=C*H*$_2$), 5.66(m, 1H, -C*H*=), 6.83-6.88(m, 4H, phenyl), 7.34(d, 2H, phenyl, J=8.8Hz), 7.69(d, 2H, phenyl, J=8.8Hz), 8.19(s, s, 1H, -C*H*=N-); ^{13}C-NMR($CDCl_3$) δ 43.18(t, -*C*H_2-), 55.20(s, 2-O*C*H_3),74.52(d, -N*C*H-), 113.72(d, phenyl), 113.85(d, phenyl), 116.89(t, =*C*H_2), 128.06(d, phenyl), 129.30(s, phenyl), 129.78(d, phenyl), 135.70(d, -*C*H=), 158.97(d, -*C*H=N-), 161.54(s, phenyl).

***N*-(2-Furylmethylidene)-1-(2-furyl)-3-buten-1-amine**: colorless liquid; 140 °C/0.2 mmHg(Kugelrohr distillation); IR(neat) 1646 cm^{-1} ($\nu_{C=N}$); ^{1}H-NMR($CDCl_3$) δ 2.80(m,2H, -C*H*$_2$-), 4.43(t, 1H, -NC*H*-, J=6.9Hz), 5.02-5.14(m, 2H, =C*H*$_2$), 5.69-5.84(m, 1H, -C*H*=), 6.25(d, 1H, furyl, J=3.5Hz), 6.31(dd, 1H, furyl, J=3.0, 2.0Hz), 6.45(dd, 1H, furyl, J=3.5, 1.5Hz), 6.76(d, 1H, furyl, J=3.0Hz) 7.35(d, 1H, furyl, J=2.0Hz), 7.50(d, 1H, furyl, J=1.5Hz), 8.06(s, 1H, -C*H*=N-) ; ^{13}C-NMR($CDCl_3$) δ 38.91(t, -*C*H_2-), 67.77(d, -N*C*H-), 106.48(d, furyl), 110.16(d, furyl), 111.65(d, furyl), 114.80(d, furyl), 117.55(t, =*C*H_2), 134.71(d, -*C*H=), 141,86(d, furyl), 144.91(d, furyl), 150.06(d, -*C*H=N-), 151.27(s, furyl), 154.94(s, furyl), mass spectrum (electron impact) m/e. 215(M^+, 1.2), 174(M^+-C_3H_5, base peak).

***N*-Pentylidene-octen-4-amine**: colorless liquid; IR(neat) 1653 cm^{-1} ($\nu_{C=N}$); 120 °C / 5.0 mmHg(Kugelrohr distillation); ^{13}C-NMR($CDCl_3$) δ 13.9(q, -*C*H_3), 14.0(q, -*C*H_3), 22.3(t, -*C*H_2-), 22.5(t, -CH_2-), 28.6(t, 2C, -CH_2-), 35.3(t, 2C, -CH_2-), 40.9(t, CH_2-), 70.9(d, -N*C*H-), 116.4(t, =*C*H_2), 136.0(d, -*C*H=), 164.0(d, -N=*C*H-).

Isopropyl phenyl ketimine: colorless solid; 170 °C / 5 mmHg(Kugelrohr distillation); IR(neat) 3200 cm^{-1} (br, ν_{N-H}), 1616 cm^{-1} (s, $\nu_{C=N}$); ^{1}H-NMR($CDCl_3$) δ 1.18(d, 6H, -C*H*$_3$, J=6.8Hz), 3.17(septet, 1H, -C*H*-, J=6.8Hz), 7.37-7.67(m, 6H, phenyl, N*H*); ^{13}C-NMR($CDCl_3$) δ 20.21(q. -*C*H_3), 33.79(d, -*C*H-), 126.44(d, phenyl), 128.48(d, phenyl), 129.93(d, phenyl), 139.57(s, phenyl),184.29(s, -*C*=N-).

***O*-Allyl benzaldoxime**: colorless liquid; 120 °C/5 mmHg(Kugelrohr distillation); IR(neat) 1645cm^{-1} ($\nu_{C=N}$); ^{1}H-NMR($CDCl_3$) δ 4.67(ddd, 2H, -OC*H*$_2$-, J=5.6, 1.5, 1.2Hz), 5.22-5.39(m, 2H, =C*H*$_2$), 5.98-6.12(m, 1H, -C*H*=), 7.33-7.36(m, 3H, phenyl), 7.55-7.59(m, 2H, phenyl), 8.11(s, 1H, -C*H*=N-); ^{13}C-NMR($CDCl_3$) δ 74.9(t, -O*C*H_2-), 117.6(t, =*C*H_2), 126.8(d, phenyl), 128.4(d, phenyl), 129.5(d, phenyl), 131.9(s, phenyl), 133.9(d, -*C*H=), 148.5(d, -*C*H=N-), mass spectrum (electron impact) 161(M^+, 30.5), 160(M^+-1, 27.6), 77(Ph^+, 54.6), 41($C_3H_5^+$, base peak).

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General Conclusion

Transition-metal complex-catalyzed novel transformation of nitroarenes and oximes by deoxygenation using carbon monoxide are described in the previous chapters.

Part I dealt with palladium and ruthenium complex-catalyzed reductive *N*-heterocyclization of *ortho*-substituted nitroarenes using carbon monoxide as a deoxygenating agent.

In chapter 1, palladium complex-tin(II) chloride system-catalyzed reductive *N*-heterocyclization of *N*-(2-nitrobenzylidene)amines into 2*H*-indazole derivatives was developed. Among the catalyst systems examined, $PdCl_2(PPh_3)_2$-$SnCl_2$ system showed the highest catalytic activity. By the reductive *N*-heterocyclization of *N*-(2-nitrobenzylidene)propylamine at 100 °C for 16 h under 20 $kgcm^{-2}$ of initial carbon monoxide pressure, 2-propyl-2*H*-indazole was obtained in 83% yield. The present reaction may be rationalized by assuming a nitrene intermediate. First, deoxygenation of the nitro group in *N*-(2-nitrobenzylidene)amine by carbon monoxide would occur to give the corresponding nitrene intermediate. This electrophilic nitrene could attack the nitrogen atom of the imino substituent to give 2*H*-indazole. Noteworthy is that the present reaction offers a novel method for the selective nitrogen-nitrogen bond forming reaction.

Chapter 2 showed a successful application of the above mentioned catalyst system ($PdCl_2(PPh_3)_2$-$SnCl_2$) to the selective synthesis of indoles from *o*-nitrostyrenes. For example, 2-phenylindole was obtained in 75% yield by the reductive *N*-heterocyclization of *o*-nitrostilbene. After the reaction, carbon dioxide in a gas phase was detected in 141% yield based on the *o*-nitrostyrene charged. The reaction sequences of *o*-aminostilbene, deuterium labeled *o*-nitrostyrene (β,β-dideuterio-α-methyl-*o*-nitrostyrene) and β,β-dimethyl-*o*-

nitrostyrene strongly suggested that the present reaction would proceed via a nitrene intermediate. When β,β-dimethyl-*o*-nitrostyrene was employed in the present reaction, 2,3-dimethylindole was obtained in 52% yield via reductive *N*-heterocyclization and subsequent rearrangement of the methyl substituent. This rearrangement seems to proceed owing to the stabilization of the cationic carbon (α-position of starting *o*-nitrostyrene), which was generated by the electrophilic intramolecular cyclization of the nitrene intermediate.

In chapter 3, ruthenium and platinum complex-catalyzed reductive *N*-heterocyclization of *N*-(2-nitrobenzoyl)amides to 4(3*H*)-quinazolinone derivatives was successfully developed. For example, azacyclooctano[2,1-*b*]-4(3*H*)-quinazolinone was synthesized in 94% isolated yield from the reductive *N*-heterocyclization of *N*-(2-nitrobenzoyl)-2-azacyclooctanone using $Ru_3(CO)_{12}$ catalyst (3.3 mol%) at 140 °C for 16 h under 40 $kgcm^{-2}$ of initial carbon monoxide pressure. The present reaction can be applied to the one-pot synthesis of indolo[2,1-*b*]quinazoline-6,12-dione, which is well-known as antibiotic tryptanthrine. Furthermore, when an excess amount of, *i.e.*, three equivalent of pentacarbonyliron ($Fe(CO)_5$) was employed in the reaction of *N*-(2-nitrobenzoyl)-2-azacycloheptanone, the corresponding 4(3*H*)-quinazolinone was also obtained in 51% yield even under an argon atmosphere. This result clearly indicated that carbon monoxide pressure is not always essential for the present reaction, if an enough of transition-metal carbonyl complexes is employed. The present reaction can also be rationalized by assuming a similar transition-metal nitrene intermediate.

In chapter 4, $PdCl_2(PPh_3)_2$-$MoCl_5$ catalyzed intermolecular reductive *N*-heterocyclization of 2-nitrobenzaldehydes or 2-nitrophenyl ketones with formamide to quinazoline derivatives was explored. For example, quinazoline was obtained in 46% yield by the reaction of 2-nitrobenzaldehyde with formamide. In the absence of both palladium complex and $MoCl_5$, 2-

nitrobenzaldehyde reacted with formamide to give the corresponding 2-nitrobenzaldiformamide. When the generated 2-nitrobenzaldiformamide was treated with a catalytic amount of $PdCl_2(PPh_3)_2$-$SnCl_2$ at 100 °C for 16 h under carbon monoxide pressure, quinazoline was actually obtained. So the present reaction would proceed via 2-nitrobenzaldiformamide as one of the possible intermediates.

Part II dealt with ruthenium complex-catalyzed novel transformations of oximes by deoxygenative reduction using carbon monoxide.

In chapter 5, ruthenium complex-catalyzed selective deoxygenation of ketoximes to ketimines was fully investigated. $Ru_3(CO)_{12}$ showed a high catalytic activity for the selective deoxygenation of various ketoximes to the corresponding ketimines under carbon monoxide pressure (20 $kgcm^{-2}$). For the deoxygenation of propiophenone oxime, ethyl phenyl ketimine was obtained in 100% yield. After the reaction, carbon dioxide was detected in 85% yield based on the amount of propiophenone oxime. In the case of acetoxime, the deoxygenation and subsequent trimerization of the generated imine via deamination reaction proceeded to give 2,2,4,4,6-pentamethyl-2,3,4,5-tetrahydropyrimidine in 38% yield. On the other hand, aldoximes were only dehydrated to nitriles under the same reaction conditions.

Chapter 6 described ruthenium complex-catalyzed selective deoxygenation of amidoximes. For example, benzamidoxime was treated with a catalytic amount of $Ru_3(CO)_{12}$ at 80 °C for 5h under 5 $kgcm^{-2}$ of carbon monoxide pressure to afford benzamidine in 82% yield. Furthermore, when the present deoxygenation of amidoximes was carried out in the presence of 1,3-dicarbonyl compounds such as acetylacetone, the corresponding pyrimidine derivatives, which were the condensation products of the generated amidines with 1,3-dicarbonyl compounds, were obtained in up to 93% yield.

In chapter 7, the first example of *catalytic* allylation of the C=N bond in amidoximes via ruthenium-catalyzed deoxygenation of amidoximes was disclosed. In the presence of a catalytic amount of $Ru_3(CO)_{12}$, the reaction of 4-methoxybenzaldoxime with allyl methyl carbonate afforded *N*-(4-methoxybenzylidene)-1-(4-methoxyphenyl)-3-buten-1-amine in 74% yield. The reaction appeared to proceed through a π-allylruthenium intermediate due to its novel nucleophilicity. In contrast to the ruthenium catalyst, when a palladium or platinum catalyst was employed in the reaction of benzaldoxime with allyl methyl carbonate, the selective *O*-allylation of aldoximes smoothly proceeded through π-allylpalladium and platinum intermediates due to their normal electrophilicity.

As described above, transition-metal complex-catalyzed novel transformations of nitroarenes and oximes by deoxygenative reduction using carbon monoxide have been developed and fully investigated in this thesis. We believe that a new field of carbon monoxide, *viz.* C_1 chemistry could be explored by this study.

Finally, from a standpoint of organometallic chemistry, much attention has recently been paid to the reactivity of the transition-metal nitrene complex, which would be involved as a key intermediate in a series of the reactions described in part I. In the reactions in chapters 1 and 2, the possible nitrene intermediates apparently operate as electrophiles and in the reactions in chapters 3 and 4, they can operate as nucleophiles. Namely, this study proposes a novel *ambiphilic* reactivity of transition-metal nitrene intermediates. If this novel reactivity of the nitrene is fully characterized, further development of general and novel synthetic methods for various nitrogen chemicals can be expected in the fields of pharmacology, agriculture and chemical industry. Further study concerned with the mechanisms of the reaction and isolation of intermediates is now still continued.

List of Publications

Chapter 1 **Palladium Complex-catalysed Reductive *N*-Heterocyclization of *N*-(2-Nitrobenzylidene)amines into 2*H*-Indazole Derivatives**
Motohiro Akazome, Teruyuki Kondo, and Yoshihisa Watanabe
J. Chem. Soc., Chem. Commun. **1991**, 1466.

Chapter 2 **Novel Synthsis of Indoles via Palladium-Catalyzed Reductive *N*-Heterocyclization of *o*-Nitrostyrenes**
Motohiro Akazome, Teruyuki Kondo, and Yoshihisa Watanabe
Chem. Lett. **1992**, 769.

Chapter 3 **Transition-Metal Complex-Catalyzed Reductive *N*-Heterocycization: Synthesis of 4(3*H*)-Quinazolinone Derivatives from *N*-(2-Nitrobenzoyl)amides**
Motohiro Akazome, Teruyuki Kondo, and Yoshihisa Watanabe
J. Org. Chem. **1993**, in press.

Chapter 4 **Palladium Complex-Catalyzed Reductive *N*-Heterocyclization of 2-Nitrobenzaldehydes or 2-Nitrophenyl Ketones with Formamide into Quinazoline Derivatives**
Motohiro Akazome, Jun Yamamoto, Teruyuki Kondo, and Yoshihisa Watanabe
Submitted for publication.

Chapter 5 **Ruthenium Complex Catalyzed Selective Deoxygenation of Ketoximes to Ketimines**
Motohiro Akazome, Yasushi Tsuji, and Yoshihisa Watanabe
Chem. Lett. **1990**, 635.

Chapter 6 **Ruthenium Complex-Catalyzed Selective Deoxygenation of Amidoximes to Amidines and its Application to the Facile Synthesis of Pyrimidines**
Motohiro Akazome, Teruyuki Kondo, and Yoshihisa Watanabe
J. Mol. Catal. **1993**, in press.

Chapter 7 **Ruthenium Complex-Catalyzed Deoxygenative Allylation of Aldoximes by Allylic Carbonates: Novel Synthesis of Homoallylic Amines**
Teruyuki Kondo, Motohiro Akazome, and Yoshihisa Watanabe
Submitted for publication.

The following publications are not included in this thesis.

Lanthanide(II) Iodide Catalysed Photochemical Allylation of Aldehydes with Allylic Halides
Teruyuki Kondo, Motohiro Akazome, and Yoshihisa Watanabe
J. Chem. Soc., Chem. Commun. **1991**, 757.

Ruthenium Complex Catalyzed Intermolecular Hydroacylation and Transhydroformylation of Olefins with Aldehydes
Teruyuki Kondo, Motohiro Akazome, Yasushi Tsuji,
and Yoshihisa Watanabe
J. Org. Chem. **1990**, *55*, 1286.